Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Eli Lilly

2. **Company summary of information for patients (SIP)** from Eli Lilly

3. **Clarification questions and company responses:**
   a. Main response
   b. Addendum

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Association for Multiple Endocrine Neoplasia Disorders (AMEND)
   b. British Thyroid Foundation (BTF) and Butterfly Thyroid Cancer Trust (BTCT)

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRiG)

6. **External Assessment Report – factual accuracy check**

7. **Expert personal perspectives** from:
   a. Kirstie Purnell – patient expert, nominated by AMEND
   b. Jonathan Wadsley, Consultant Clinical Oncologist – clinical expert, nominated by Eli Lilly (company)
   c. Kee Howe Wong, Consultant Clinical Oncologist – clinical expert, nominated by Eli Lilly (company)

8. **External Assessment Group scenario analyses**

9. **External Assessment Group post-committee cost-effectiveness results for committee preferred assumptions**

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 untreated advanced thyroid cancer with *RET* alterations [ID6132]

Document B

Company evidence submission

October 2023

File name	Version	Contains confidential information	Date
ID6132_Selpercatinib_NICE _Document B_Final_27Oct23 [CON REDACTED]	Final	Yes	27/10/23

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Tables

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Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse events
AESI	Adverse events of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
ATC	Anaplastic thyroid cancer
AUC(0–24)	Area under the concentration time curve from time 0 to 24 hours
BIC	Bayesian information criteria
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
Cab	Cabozantinib
CAP	College of American Pathologists
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
cfDNA	circulating free deoxyribonucleic acid
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum drug concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
CUA	Cost-utility analysis
CYP3A4	Cytochrome P450 3A4
DCO	Data cut-off
DCR	Disease control rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOI	Digital object identifier
DOR	Duration of response
DSA	Deterministic sensitivity analysis

DSU	Decision Support Unit
DTC	Differentiated thyroid cancer
EAG	External Assessment Group
ECDRP	European Commission Decision Reliance Procedure
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EU	European Union
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D-3/5L	Euro-QoL Questionnaire 5 Dimensions 3/5 levels
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30
FISH	Fluorescent in situ hybridisation
FTC	Follicular thyroid cancer
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
ICER	Incremental cost-effectiveness ratio
Incr.	Incremental
IPD	Individual patient-level data
IRC	Independent review committee
ISO/IEC	International Organization for Standardisation/Independent Ethics Committee
ITC	Indirect treatment comparisons
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
MHRA	Medicines and Healthcare products Regulatory Agency
MKI	Multi-kinase inhibitors
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MVH	Measurement and Valuation of Health study
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National health service
NICE	National Institute for Health and Care Excellence

NMA	Network meta-analysis
NMD	Non-measurable disease
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
PCR	Polymerase chain reaction
PD	Progressive disease
PDTC	Poorly differentiated thyroid cancer
PF	Progression free
PFS	Progression free survival
PH	Proportional hazards
PK	Pharmacokinetic
PPI	Proton pump inhibitors
PPPY	Per patient per year
PR	Partial response
PRO	Patient reported outcome
Prop	Proportion
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Papillary thyroid cancer
QALY	Quality-adjusted life year
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
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RECIST v1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
RET	Rearranged during transfection
RP2D	Recommended Phase II dose
RPSFT	Rank preserving structural failure time model
RR-DTC	Radioactive iodine refractory differentiated thyroid cancer
SACT	Systemic anticancer therapy
SAE	Serious adverse event
SAS	Safety analysis set

SD	Stable disease/ Standard deviation
SFU	Safety follow-up
SLR	Systematic literature review
SmPC	Summary of product characteristics
SRC	Safety review committee
TA	Technology appraisal
TC	Thyroid cancer
TCS	Topical corticosteroids
TE	Treatment emergent
TEAE	Treatment-emergent adverse event.
TE-SAEs	Treatment-emergent serious adverse events
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
T_{max}	Time to maximum plasma concentration
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
TTD	Time to discontinuation
UK	United Kingdom
Van	Vandetanib
VEGF	Vascular endothelial growth factor
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 objective of this appraisal is to determine the clinical and cost-effectiveness of selpercatinib, with the following proposed positioning:

- For advanced rearranged during transfection (*RET)*-mutant medullary thyroid cancer (MTC) in people aged 12 years and older who require systemic therapy (and who have not previously received systemic therapy)
- For advanced *RET* fusion-positive thyroid cancer (TC) in people aged 12 years and older who require systemic therapy (and who have not previously received systemic therapy)

For the *RET*-mutant MTC population, the population of interest in this submission is narrower than the technology's full marketing authorisation for selpercatinib "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC" as this submission covers only those patients with MTC who require systemic therapy who have not previously received systemic therapy.[1]

For the *RET* fusion-positive TC population, the patient population in this submission is narrower than the technology's full anticipated marketing authorisation for selpercatinib "[redacted]", as this submission covers only those patients with TC who require systemic therapy who have not previously received systemic therapy.

Selpercatinib is already reimbursed via the Cancer Drugs Fund for the remaining populations (i.e., patients previously treated with systemic therapy) of the licensed population (NICE TA742; 'selpercatinib for treating advanced thyroid cancer with *RET* alterations').[2] Therefore, this submission considers the systemic therapy naïve setting for *RET*-altered TC and MTC only.

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

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Populations	***RET*-fusion positive TC:** Adults with untreated advanced *RET*-fusion positive thyroid cancer who require systemic therapy ***RET*-mutant MTC:** Adults and adolescents 12 years and older with untreated advanced *RET*-mutant MTC who require systemic therapy	***RET*-fusion positive TC:** Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy) ***RET*-mutant MTC:** Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)	***RET*-fusion positive TC:** NA – in line with the NICE final scope ***RET*-mutant MTC:** NA – in line with the NICE final scope
Intervention	Selpercatinib	Selpercatinib	NA – in line with the NICE final scope
Comparator(s)	***RET* fusion-positive TC:** • Lenvatinib • Sorafenib • Best supportive care (BSC) ***RET*-mutant MTC:** • Cabozantinib (adults only) • BSC	***RET*-fusion positive TC:** • Lenvatinib • BSC ***RET*-mutant MTC:** • Cabozantinib • BSC	***RET*-fusion positive TC:** In this submission, lenvatinib is positioned as the primary comparator in the TC indication, of most relevance to decision making. Clinical expert opinion obtained to support the development of this submission confirmed that lenvatinib is the predominant MKI used in UK clinical practice, due to a perceived improved efficacy and similar adverse event profile with respect to sorafenib.[3] UK clinical experts indicated for patients receiving MKIs, the vast majority (90%-95%) of patients receive lenvatinib.[3] UK clinical experts stated that sorafenib is rarely used, when compared with lenvatinib, so sorafenib is not considered a relevant comparator in this appraisal. BSC is positioned as secondary comparators in this submission. BSC is only received by patients ineligible for treatment with an MKI, including children and adolescents aged 12–17 years. Clinical expert opinion indicates that

			90–95% of patients in the TC indication would receive a MKI.[3] ***RET*-mutant MTC:** In line with the NICE final scope. In this submission, cabozantinib is positioned as the primary comparator in the MTC indication. Clinical expert opinion gained to validate the MTC treatment pathway in the UK estimated that 85–95% of individuals with advanced *RET*-mutant MTC in the UK will receive treatment with cabozantinib.[3] BSC is positioned as a secondary comparator in this submission in the MTC indication. BSC is only received by patients who are ineligible for treatment with cabozantinib, including patients who may be unable to tolerate the associated toxicity profile and children and adolescents aged 12–17 years.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rate • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	**Primary endpoints** • Best overall response (BOR) and objective response rate (ORR) **Key secondary endpoints** • Duration of response (DOR) • Time to response and time to best response • Clinical benefit rate (CBR) • OS • PFS • AEs • HRQoL	NA – in line with the NICE final scope

Abbreviations: AE: adverse event; BOR: best overall response; BSC: best supportive care; CBR: clinical benefit rate; DOR: duration of response; HRQoL: health-related quality of life; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; NA: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression free survival; *RET*: rearranged during transfection; TC: thyroid cancer; UK: United Kingdom.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and the administration requirements of selpercatinib for the treatment of systemic therapy naïve *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 a highly potent, orally available, selective small molecule inhibitor of the *RET* receptor tyrosine kinase.[1] The *RET* receptor tyrosine kinase is essential for normal development and maturation of various tissues. Chromosomal rearrangements involving in-frame fusions of *RET* with various partners can result in constitutively activated chimeric *RET*-fusion proteins. These proteins can act as oncogenic drivers, promoting cell proliferation and survival in tumour cell lines. Point mutations in *RET* can also result in constitutively activated *RET* proteins that can promote cell growth and survival in tumour cell lines.[1] Selpercatinib targeting within the kinome (the complete set of protein kinases encoded within the genome) is highly selective for *RET*, *RET*-fusion and *RET*-mutant variants.[1]
Marketing authorisation/ CE mark status	***RET*-mutant MTC** A conditional marketing authorisation application for selpercatinib for *RET*-mutant MTC was submitted to the European Medicines Agency (EMA) in December 2019. The original marketing authorisation was received in February 2021 for the treatment of *RET*-mutant MTC previously treated with systemic therapy (cabozantinib and/or vandetanib). The marketing authorisation was then expanded in September 2022 to cover both the previously treated and systemic treatment-naïve MTC populations.[4] A conditional marketing authorisation application for the treatment of systemic therapy naïve patients with *RET*-mutant MTC was also submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) via the European Commission Decision Reliance Procedure (ECDRP) route in August 2022. Marketing authorisation in this indication was granted in February 2023.[1] ***RET* fusion-positive TC** A conditional marketing authorisation application for selpercatinib for the treatment of patients with systemic therapy naïve *RET*-fusion positive TC was submitted to the EMA on September 2022, with a positive opinion from the CHMP anticipated in [redacted]. A conditional marketing authorisation application for the treatment of patients with systemic therapy naïve *RET*-fusion positive TC is planned to be submitted to the MHRA in [redacted] with approval expected in [redacted]. **Other indications** Selpercatinib is also licensed in other indications that are not within the scope of this appraisal, which have been previously evaluated by NICE.[2, 5]

Indications and any restriction(s) as described in the SmPC	As marketing authorisation for selpercatinib for the treatment of patients with systemic therapy naïve *RET*-mutant MTC was approved by the MHRA in February 2023, as described above, wording in this indication is as follows: "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC" The anticipated MHRA marketing authorisation wording for selpercatinib for the treatment of patients with systemic therapy naïve *RET*-fusion positive TC is: "[redacted]" **Contraindications** Hypersensitivity to the active substance or to any of the excipients[1]
Method of administration and dosage	The recommended dose of selpercatinib based on weight is: • Less than 50 kg: 120 mg orally, twice daily • 50 kg or greater: 160 mg orally, twice daily Treatment should be continued until disease progression or unacceptable toxicity[1]
Additional tests or investigations	An accurate and validated assay for the presence of a *RET* gene fusion (non-small cell lung cancer [NSCLC] and TC) or mutation (MTC) 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, with molecular testing recommended to be undertaken at diagnosis of advanced disease.[6] 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 2023/2024 National Genomic Test Directory for Cancer, with NGS panel testing now available on the National Health Service (NHS) for all solid and blood cancers. In England, this transition to NGS testing means it will be possible to test for *RET* rearrangements routinely alongside other oncogenic drivers in a standardised manner across different centres.[7, 8]
List price and average cost of a course of treatment	The list price for available formulations and pack sizes of selpercatinib are provided below: • 56 capsules of 40 mg selpercatinib: £2,184.00 • 168 capsules of 40 mg selpercatinib: £6,552.00 • 56 capsules of 80 mg selpercatinib: £4,368.00 • 112 capsules of 80 mg selpercatinib: £8,736.00 At list price, the cost of a 28 day cycle of selpercatinib is £8,736.00.
PAS (if applicable)	A confidential Patient Access Scheme (PAS) offering a discount of [redacted]% has been provided with this submission. The PAS provides a 168-capsule bottle of 40 mg selpercatinib and a 112-capsule bottle of 80 mg selpercatinib at a net price of £[redacted] and £[redacted], respectively.

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; EU: European Union; FISH: fluorescent in situ hybridisation; MHRA: Medicines and Healthcare products Regulatory Agency; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; NGS: next generation sequencing; NSCLC: non-small cell lung cancer; PAS: patient access scheme; *RET*: rearranged during transfection; SmPC: summary of product characteristics; TC: thyroid cancer.
Source: Drilon *et al.* (2018)[9], Mulligan *et al.* (2018)[10]; MHRA. Selpercatinib SmPC. 2023.[1]

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

Summary of thyroid cancer and medullary thyroid cancer

- Thyroid cancer is a rare type of cancer that accounts for approximately 1% of all new cancer cases in the UK.[11]
- There are five major histological subtypes of thyroid cancer. Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are classified as differentiated thyroid cancers (DTC). PTC is the most common, accounting for around 90% of all TCs, with FTC accounting for just over 4% of all TCs. Hürthle cell TC is a rare form of TC accounting for approximately 2% of all TCs and anaplastic, or undifferentiated, thyroid cancer (ATC) accounts for less than 1%.[12]
    - All subtypes of thyroid cancer arising in the follicular cells (i.e., papillary TC [PTC], follicular TC [FTC], Hürthle cell TC and ATC), are hereafter collectively referred to as 'TC'.
- MTC is an aetiologically distinct type of thyroid cancer which develops in non-follicular cells. MTC accounts for approximately 4% of all thyroid cancer cases.[13]
    - TC and MTC collectively are, hereafter, referred to as 'thyroid cancer'.
- Thyroid cancer has been associated with specific genetic variations. *RET* alterations vary in prevalence depending on the histological subtype of thyroid cancer. *RET* fusions have been identified in ranges from 5–40% in PTC, but they are uncommon in other types of follicular TCs.[10, 14] In MTC, nearly all patients with hereditary MTC (accounting for approximately 25% of MTC cases) have a *RET* mutation; MTC arises sporadically in about 75% of cases and *RET* somatic mutations occur in about 40–50% of sporadic MTC.[15]
- While TC is associated with a generally good prognosis, metastatic TC demonstrates a poor one-year survival rate of 77%.[16] Survival is dependent on subtype of TC; five-year survival for distant stage TC ranges from 74% for PTC to just 4% for distant stage ATC.[17]
- In addition to facing a poor prognosis, patients with TC have poorer health-related quality of life (HRQoL) than the general population due to a substantial symptom and disease burden.[18, 19] Key concerns include fatigue, pain, fear of recurrence, physical and mental exhaustion, employment, and lumps in the neck.[20] MTC is associated with additional debilitating symptoms, including severe diarrhoea, Cushing syndrome, bone pain, lethargy and weight loss, as well as distant metastases.[21, 22] These symptoms may lead to workplace absence and lost productivity.[23]

Summary of the diagnostic and treatment pathway

- Confirmation of *RET*-testing will be required to determine eligibility for selpercatinib. NGS panel testing now routinely available through the NHS shall expedite the diagnostic process, allowing clinicians to prescribe targeted therapies, such as selpercatinib, with greater ease and convenience.[6, 8]
- For patients with MTC, following surgery, cabozantinib is recommended for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC (TA516).[24] Cabozantinib represents the only treatment available for patients with untreated advanced MTC, so patients ineligible for treatment with cabozantinib (including adolescents aged 12–17 years old) face BSC as the only treatment option.
- Following surgery and treatment with radioactive iodine, lenvatinib and sorafenib are the only treatments recommended for the first-line treatment of DTC which is classified as progressive, advanced or metastatic that was not responsive to radioactive iodine in adult patients that are tyrosine kinase inhibitor (TKI)-naïve (TA535). During interviews conducted to support this appraisal, UK clinical experts stated that for patients receiving MKIs, the vast majority (90–95%) of patients receive lenvatinib.[3, 25, 26]
- For patients ineligible for treatment with lenvatinib or sorafenib, such as patients with ATC or adolescents aged 12–17 years old BSC represents the only remaining option. Selpercatinib is

available for patients with ATC who have not received prior MKI therapy, however it is only available via the Cancer Drugs Fund (CDF).[27]

Positioning of selpercatinib and comparators

- The proposed positioning of selpercatinib in this submission is for "people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)" and "people aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)".
- The relevant comparators for selpercatinib in the advanced *RET*-mutant MTC population are cabozantinib and BSC (for patients who are ineligible for cabozantinib)
    - During interviews conducted to support this submission, UK clinical experts stated that 80–90% of patients with advanced *RET*-mutant MTC currently receive cabozantinib, so cabozantinib is considered the primary comparator to selpercatinib in this patient population.[3]
- The relevant comparators for selpercatinib for patients with advanced *RET*-fusion positive TC are lenvatinib and BSC (for patients who are ineligible for MKI treatment).
    - During interviews conducted to support this submission, UK clinical experts stated that the majority of patients that receive an MKI receive lenvatinib (~90–95%).[3, 28] As such, lenvatinib is considered the primary comparator to selpercatinib in the advanced *RET*-fusion positive TC population and sorafenib is not considered a relevant comparator.
- Patients with advanced thyroid cancer face a poor prognosis despite currently available systemic treatments in the UK. As such, whilst selpercatinib is currently reimbursed via the CDF in the second line setting for TC and MTC, there is a high unmet need for an effective treatment that is available sooner in the treatment pathway, to maximise the treatment benefit to patients.
- In addition, with highly specific and potent targeting of *RET* alterations, selpercatinib may also offer reduced AEs when used as a treatment for *RET*-altered thyroid cancer when compared to MKIs, and an effective treatment option for patients with who cannot receive currently available treatments and therefore receive BSC.

B.1.3.1 Disease overview

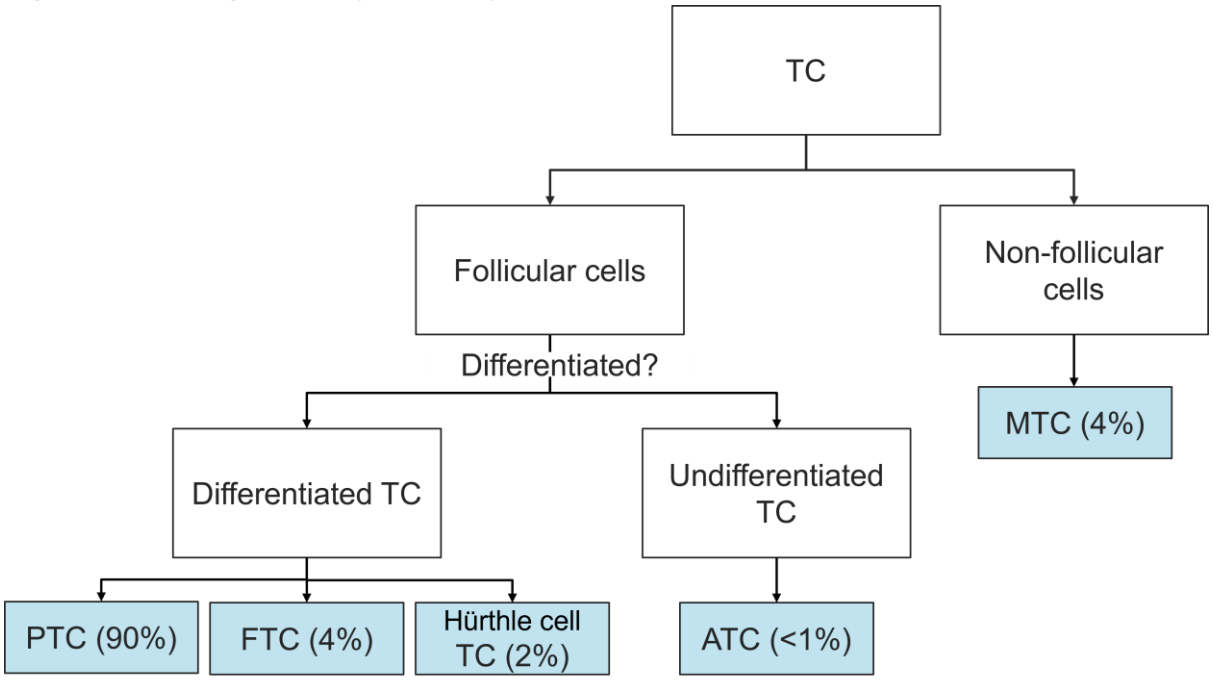
This submission focuses on the following indications:

- People aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)
- People aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)

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.[29] The thyroid is part of the endocrine system, and it secretes hormones to regulate a variety of vital bodily functions including metabolism, heart rate, central and peripheral nervous systems among others.[30] It is made up primarily of two types of cell: follicular cells, which produce thyroid hormones (tri-iodothyronine [T3] and thyroxine [T4]); and non-follicular C cells, which produce calcitonin to regulate levels of calcium in the blood.[31]

There are five major histological subtypes of thyroid cancer: papillary, follicular, Hürthle cell, anaplastic (or undifferentiated) and medullary, as illustrated in Figure 1.

Figure 1: Histological subtypes of thyroid cancer



Estimates for the prevalence of MTC cases corresponds to the adult population of patients with TC.
Abbreviations: ATC: anaplastic thyroid cancer; FTC: follicular thyroid cancer; MTC: medullary thyroid cancer; PTC: papillary thyroid cancer; TC: thyroid cancer.
Source: Cancer Research UK,[12]; Roy et al. 2013.[13]

Classification of thyroid cancer subtype is dependent on whether the cancer arises in the follicular or non-follicular cells.[31, 32] Papillary, follicular, Hürthle cell TCs and ATCs form in the follicular cells, whilst MTC forms in the non-follicular cells and is associated with additional symptoms, such as persistent diarrhoea or flushing of the face due to dysregulation of calcitonin.[29, 32] All subtypes of thyroid cancer arising in the follicular cells (i.e., papillary TC [PTC], follicular TC [FTC], Hürthle cell TC and ATC), are hereafter collectively referred to as 'TC', whilst MTC and TC are collectively hereafter referred to as 'thyroid cancer'.

PTC and FTC are classified as DTC and are the most common TCs, accounting for around 90% and 4% of all TC cases, respectively.[12] Hürthle cell cancers are a rare type of DTC accounting for approximately 2% of TC cases.[12] ATC accounts for less than 1% of all TC cases. MTC is also a rare form of thyroid cancer, accounting for approximately 4% of all thyroid cancer cases.[13]

MTC can be further divided into two classifications: sporadic MTC, primarily affecting adult populations, and hereditary MTC, caused by inherited cancer syndromes known as multiple endocrine neoplasia type 2 syndromes (MEN2), which may have an early onset.[32] MEN2 is further classified into two subtypes, MEN2A and MEN2B, based on disease severity and associated phenotypes. The more common subtype, MEN2A, represents >95% of cases, with the less common and clinically more severe MEN2B subtype associated with earlier disease onset and more aggressive disease.[10]

RET alterations in thyroid cancer

Thyroid cancer has been associated with specific genetic variations that either activate oncogenes or turn off tumour suppressor genes. The *RET* oncogene was first discovered in

1985, and is now recognised in a diverse range of tumour types with implications for diagnosis, prognosis and disease management decisions.[10] Activation of the *RET* oncogene occurs via two major mechanisms: *RET* fusions and *RET* point mutations.[33] *RET* fusions, alterations, or point mutations can occur in specific histological subtypes such as MTC and PTC resulting in oncogenic activation.[32]

Estimates for the prevalence of oncogenic *RET* fusion proteins in PTC, based on aetiological factors, vary significantly by geography and by study. The reported prevalence of *RET* fusions range from 5–40% of all PTC cases across the published literature.[10, 14] In a large study including 496 patients with PTC, *RET* fusions were identified in 6.8% of the patient population.[34] *RET* alterations in *RET* fusion-positive PTC, termed *RET*/PTC, are most typically acquired during a person's lifetime.[15] 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.[35]

RET fusions are uncommon in TC subtypes other than PTC; in particular, FTC, the other major type of differentiated TC, is generally negative for *RET* fusions. Poorly differentiated thyroid cancer (PDTC) and ATC may derive from pre-existing differentiated carcinomas, including PTC, and therefore a subset may inherit *RET* fusions.[36] 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.[37] Similarly, in a more recent study, 5.9% of PDTC but no cases of ATC harboured *RET* rearrangements, suggesting that *RET* fusion-positive PTCs rarely progress to ATC.[38] Other oncogenic mutations have been implicated in papillary, follicular and anaplastic TCs, such as *TRK*, *RAS*, *BRAF*, *PPARG* and *p53*.[39] There is currently no consensus regarding the impact of *RET*-fusions on prognosis for patients with TC.[26, 40-42]

RET alterations are more commonly observed in MTC; of the approximately 25% of MTC cases that are hereditary, almost 100% are associated with mutations of the *RET* gene, while *RET* somatic mutations occur in about 40–50% of sporadic MTC, which accounts for approximately 75% of all MTC cases.[15] For patients with the hereditary subtype MEN2B syndrome, the mutation of highest risk is the M918T, which is associated with the earliest onset and most aggressive phenotypes.[10, 32] For the more common subtype, MEN2A, mutations arise from substitutions of cysteine residues in the *RET* extracellular domain (C609, C611, C618, C620, C634).

In individuals with the most common MEN2A mutation, C634R, and the MEN2B A883F mutations, prognosis is considered poor. The remaining, so-called 'moderate risk' *RET* mutations may be associated with later or more variable age of onset.[10] Somatic mutations of *RET* (mainly M918, but also including E768 and V804) are found in a subset of sporadic MTC cases and correlate with a poor prognosis versus *RET* wild type tumours.[10, 32]

Epidemiology of thyroid cancer

The World Health Organization reports thyroid cancer as one of the top 10 cancers in terms of mortality rate and age-standardised incidence worldwide.[43] In 2020, global estimates for the number of new cases of thyroid cancer were around 449,000 for women and 137,000 for men, corresponding to age-standardised incidence rates of 10.1 per 100,000 women and 3.1 per 100,000 men.[44] In the UK specifically, the 5-year prevalence (all ages) of thyroid cancer was

estimated to be 19,138 (28.7/100,000) in 2018.[45] In the UK, thyroid cancer is the 20th most common cancer, accounting for 1% of all new cancer cases with approximately 3,900 new cases every year between 2016–2018.[11]

Over the last three decades, the incidence of thyroid cancer has increased by 175% and is projected to rise by 74% between 2014 to 2035.[11] This increase may in part be attributed to changes in pathological criteria and improved detection of thyroid cancer cases due to the more widespread use of detection techniques such as ultrasound and fine needle biopsies.[46, 47] Incidence rates for thyroid cancer in the UK are highest in people aged 65 to 69, and incidence is higher in females than males (72% of thyroid cancer cases in the UK are in females, and 28% are in males).[11, 48]

Disease mortality

Mortality in advanced thyroid cancer and medullary thyroid cancer

This submission focuses on advanced *RET* fusion-positive TC and *RET*-mutant MTC. While thyroid cancer is generally associated with a good prognosis (a five-year survival rate in the UK of 85–90%, and a 10-year survival rate of 84%), advanced stage thyroid cancer is associated with a poorer prognosis; patients with Stage IV disease face a one-year survival rate of 77%.[11, 16, 49] Survival rates differ between subtypes of advanced thyroid cancer, with five-year survival rates of 74% for distant stage PTC, 67% for distant stage FTC, 43% for distant stage MTC and only 4% for distant stage ATC.[17]

Distant metastases occur in 4–15% of patients with thyroid cancer, with the more aggressive forms tending towards a higher chance of metastases and the lungs being the most commonly affected organ.[50] Metastases to the central nervous system (CNS) are unusual in thyroid cancer, occurring in around 1% of patients with DTC and MTC, however they can cause acute disabling symptoms and a marked reduction in survival.[50] For patients with DTC, median survival estimates for patients with brain metastases range from 7.1–19.0 months and higher survival is reported for patients treated with MKIs.[51]

Any stage MTC is associated with a higher mortality rate than DTC, with a five-year survival of 70% in men and 75% in women.[49] The two forms of MTC, sporadic and hereditary, are associated with different disease risk levels.[10] Sporadic *RET* mutations correlate with a more aggressive disease phenotype,[15] while hereditary MTC severity ranges depending on the specific mutation.[15]

Mortality in RET-altered thyroid cancer and medullary thyroid cancer

As noted above, contradictory findings area available in the published literature regarding whether *RET*-fusion positive TC is associated with a worse prognosis when compared to *RET* wild-type TC tumours.[26, 42] Relative tumour aggressiveness has been associated with different *RET*/PTC family members and *RET*/PTC fusions are less common in the indolent follicular variant of PTC relative to other histologic subtypes.[10] However, 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.[40, 41] *RET*-fusion-driven tumours have also been observed with higher likelihoods of distant metastasis.[52] Findings refuting these data have been reported, however, and there is

therefore no consensus on whether *RET*-fusion positive TC is associated with a worse prognosis when compared to forms of TC without *RET*-fusions.[26, 42]

In contrast, somatic mutations of *RET* correlate with a poor prognosis versus *RET* wild-type tumours.[10, 32] A study of 100 patients with sporadic MTC 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).[53] Survival curves for patients with MTC also showed a significantly lower proportion of patients alive in the group with *RET* mutations compared to those without *RET* mutations (p=0.006).[53] Overall, data in the published literature suggest that *RET* mutations in MTC are associated with a poorer prognosis when compared with wild-type MTC.

Survival with multi-kinase inhibitor treatment

For MTC, the only first-line systemic treatment recommended for use in the UK is cabozantinib.[24] In the EXAM trial, patients treated with cabozantinib showed a 5.5 month increase versus placebo in median OS of 26.6 vs 21.1 months.[54] Current systemic treatments available in the UK for iodine-refractory, systemic therapy naïve TC include the MKIs, lenvatinib and sorafenib.[25] In a systematic literature review (SLR) of these treatments, median OS was estimated to be between 31.8 and 41.6 months for patients receiving lenvatinib, and between 23.0 and 39.4 months for sorafenib.[55]

Disease burden and health-related quality-of-life impact of thyroid cancer and medullary thyroid cancer

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.[56]

MTC presents similarly to PTC, with the most common primary presentation of sporadic MTC being 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.[21] Severe diarrhoea may be debilitating and can lead to problems associated with nutrition. Distant metastases may result in additional symptoms including spinal cord compression, bone fracture, bronchial obstruction and pain.[22] Debilitating symptoms associated with MTC (for example, severe diarrhoea) may lead to workplace absence and lost productivity.[23]

The humanistic burden of RET-altered thyroid cancer is not well described in the published literature, with the majority of humanistic burden studies conducted in patients with MTC and PTC regardless of RET status. Based on the available literature, patients with PTC have poorer 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.[18] 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.[20] A recent cross-sectional study of 114 female DTC survivors demonstrated a significant worsening of every aspect of the Short Form 36 (SF-36) questionnaire

evaluating HRQoL compared to a control group of healthy individuals. Additionally, increased anxiety and depression was observed in the DTC group, with time since diagnosis not observed to affect HRQoL results.[19]

The patient expert consulted as part of the NICE evaluation of lenvatinib and sorafenib for treating DTC (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.[25] The potential for diagnosis of thyroid cancer in early adulthood, along with associations of more aggressive disease and poorer outcomes in advanced stage thyroid cancer, may have severe impacts on patient mental health, was noted by patient experts in NICE TA742 and subsequently acknowledged by the committee.[2]

Additionally, patient experts consulted as part of NICE TA742 noted that a devastating aspect of *RET*-altered TC and MTC is the relative lack of treatment options. This was highlighted in particular for *RET*-mutant MTC. For RET-altered TC and MTC, treatment options are limited to generally poorly-tolerated MKIs, which are only available to slow progression of disease and they are often accompanied by post-surgical complications. This may have a substantial effect on patients' health-related quality of life (HRQoL) and mental health.[2] Furthermore, it is likely that patients who do not respond to, are contraindicated to or do not tolerate treatment with a MKI have equally severe, if not worse HRQoL outcomes. 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 to or worse than patients with thyroid cancer as a whole.

Economic burden

There are a lack of published data on the economic burden of *RET*-altered thyroid cancer. However, thyroid cancer more broadly is a costly, resource-intensive disease, and costs and use of healthcare resources increase with advanced disease compared to early-stage disease.

In a US study, approximately 66% of all patients diagnosed with thyroid cancer had at least one thyroid cancer-related hospitalisation post-diagnosis, with an average of 3 days' hospital stay.[57] 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.[57] 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.[58] A 2023 retrospective study collecting cost data over 2011–2015 for patients with thyroid cancer in France estimated a mean cost per capita of €6,248, culminating in a total cost of €203.5 million for the management of patients with thyroid cancer patient management (€154.3 million for women, €49.3 million for men).[59] Overall, thyroid cancer is identified as a resource intensive disease, representing an important economic burden on healthcare systems.

Thyroid cancer may also have a considerable economic burden on patients. Difficulty associated with 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.[20] 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, supported by a subsequent US based review estimating a bankruptcy incidence for patients with thyroid cancer reaching 4.39 fold higher than a control

population of individuals.[60, 61] 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.[62] Financial toxicity introduced upon diagnosis of thyroid cancer has been associated with poorer HRQoL in patients, which can worsen burden of disease. For individuals experiencing employment difficulties as a result of their cancer, worse fatigue, pain interference and reduced social functioning have been reported.[63]

B.1.3.2 Selpercatinib

Selpercatinib is a highly potent, orally available, selective small molecule inhibitor of the *RET* receptor tyrosine kinase.

Selpercatinib is currently recommended by NICE for:

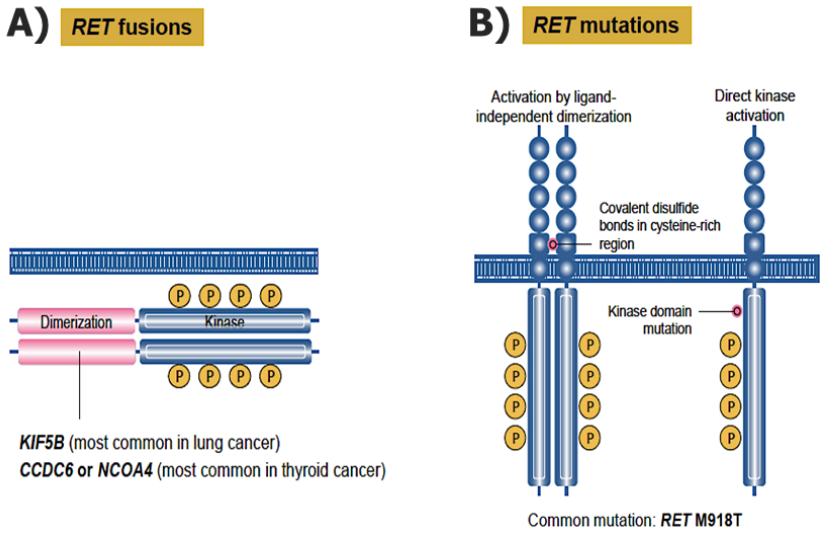
- Adults with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with sorafenib and/or lenvatinib (TA742)[2]
- People 12 years and older with advanced *RET*-mutant MTC who require systemic therapy after cabozantinib and/or vandetanib (TA742)[2]

The anticipated future licensed indication for selpercatinib, of relevance to the TC population, covered by this submission is "[redacted]". The licensed indication for the MTC population covered by this submission is "as monotherapy in adults and people aged 12 years and over with advanced *RET*-mutant MTC".

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.[10] 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 2A). Point mutations in *RET* can also result in constitutively activated *RET* proteins that can promote cell growth and survival in tumour cell lines (Figure 2B).[1]

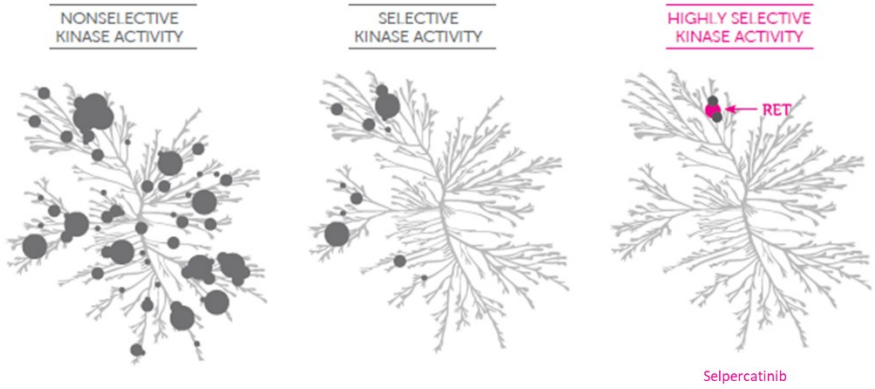
Selpercatinib targeting within the kinome (the complete set of protein kinases encoded within the genome) is displayed in Figure 3. In contrast to MKIs, which are non-selective and thus can be associated with off-target effects, selpercatinib is highly selective for *RET*, *RET*-fusion and *RET*-mutant variants.[1]

Figure 2: 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)[9]

Figure 3: Kinome selectivity of selpercatinib



Abbreviations: RET; rearranged during transfection
Source: Drilon et al. (2018)[9]

B.1.3.3 Clinical pathway of care

Treatment guidelines for the management of TC in the UK include those published by NICE (NG230)[64], the UK National Multidisciplinary Guidelines and the British Thyroid Association.[27, 39] Currently, the treatments that have been recommended by NICE for the treatment of progressive, locally advanced, or metastatic TC include the MKIs lenvatinib and sorafenib for treating DTC after radioactive iodine (TA535)[25] and cabozantinib for treating MTC (TA516).[24] NICE also evaluated vandetanib for treating MTC (TA550), and cabozantinib for the first-line treatment of DTC (ID4046). However, a negative recommendation was issued for vandetanib in MTC, while the appraisal for cabozantinib is currently ongoing with a negative draft recommendation.[28, 65]

Selpercatinib has already been evaluated by NICE and subsequently recommended for use within the CDF for the treatment of advanced *RET* fusion-positive TC in adults who need

systemic therapy after sorafenib or lenvatinib and advanced *RET*-mutant MTC in people 12 years and older who need systemic therapy after cabozantinib or vandetanib (TA742).[2] As part of this, selpercatinib can also be used in patients with ATC who have not previously any prior systemic therapy.[66]

As previously outlined in Section B.1.3.1, all subtypes of DTC (PTC, FTC and Hürthle cell TC) along with ATC, collectively referred to as 'TC', arise in follicular cells of the thyroid. MTC is an aetiologically distinct disease arising in non-follicular cells.[31, 32] For this reason, the treatment pathways for TC and MTC differ and are presented separately in the following sections.

RET testing in the UK

Confirmation by *RET*-testing will be required to determine eligibility for selpercatinib. In England, key oncogenic drivers previously used single gene FISH testing, performed on biopsy samples sequentially increasing the time taken to make a molecular diagnosis. However, the current transition to NGS, completed in Genomic Hubs, will mean a panel of genetic mutations, rearrangements and fusions (including *RET*-fusions) can be identified.[6, 8] NGS panel testing for common oncogenic drivers (including *RET*) are now available on the NHS for all types of thyroid cancer, as listed in the National Genomic Test Directory, expediting the diagnostic process and allowing clinicians to use targeted therapies, like selpercatinib, with fewer barriers.[7]

Medullary thyroid cancer

Medullary thyroid cancer diagnostic pathway

As outlined in Section B.1.3.1, 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.[27]

Ultrasonography is routinely used to evaluate thyroid nodules. The initial diagnosis of MTC 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 MTC and to discover atypical cells of undetermined significance.[56]

Various additional tests can be reviewed to confirm a differential diagnosis, including imaging studies (CT scans, MRI tests, and positron emission tomography/computed tomography scans) and blood tests (thyroid-stimulating hormone [TSH], thyroglobulin, thyroglobulin antibodies, and T3 and T4 tests).[64, 67] These tests in combination will determine the histology, size, stage and extension of the tumour, which in turn will determine the appropriate treatment strategy.[27] 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.[27, 64]

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

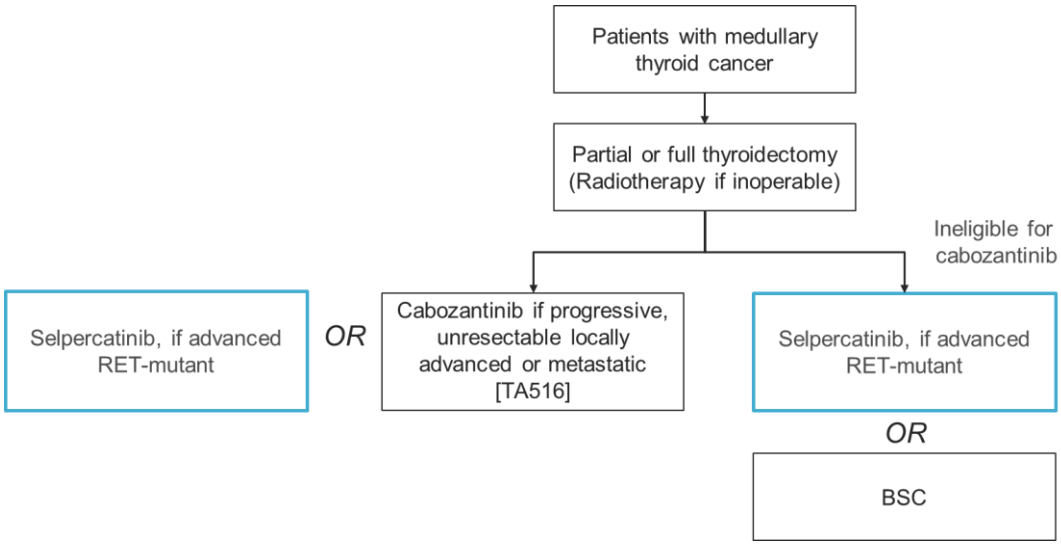
Medullary thyroid cancer treatment pathway

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.[39] 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.[27] Furthermore, prophylactic thyroidectomy should be offered to *RET*-positive family members.[27]

Cabozantinib is the only recommended treatment in the UK for progressive, unresectable locally advanced or metastatic MTC in adults (TA516).[24] Consequently, BSC is the only option for patients ineligible for treatment with cabozantinib, including adolescents that are not eligible for treatment with cabozantinib. However, during interviews to support his submission, UK clinical experts stated that approximately 80–90% of patients with advanced *RET*-mutant MTC receive cabozantinib.[3] At present there are no *RET*-specific treatments available for use in the UK for patients with MTC who have not previously received systemic therapy.

The proposed treatment pathway and positioning of selpercatinib for adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy and have not previously received systemic therapy is outlined in Figure 4. This treatment pathway was validated as representative of UK clinical practice by UK clinical experts during interviews to support this submission.[3]

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



Treatments recommended by NICE via the CDF are not represented on the above treatment pathway figure as they are not considered to be routinely available in UK clinical practice.
Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; *RET*: rearranged during transfection; TA: technology appraisal.

Unmet need in medullary thyroid cancer

Distant stage MTC is associated with a notably poor five-year survival rate of 43%, with somatic mutations of RET correlated with a poor prognosis when compared to RET wild type tumours.[10, 32] While findings are not definitive, *RET* mutations in people with advanced MTC have been associated with more aggressive disease and poorer outcomes for patients, and this was supported by clinical expert opinion during the NICE appraisal TA742.[2]

In the EXAM trial, patients treated with cabozantinib showed an improvement in median OS versus placebo (26.6 versus 21.1 months), and the OS benefit was greater in patients with *RET* M918T-positive disease compared to wild-type RET disease (44.3 versus 18.9 months); this demonstrates the benefit of targeting *RET* in this patient population.[54] However, although improved versus placebo, OS for patients receiving treatment with cabozantinib is still comparatively poor. Furthermore, cabozantinib is recommended only for adults (TA516), leaving BSC as the only remaining treatment option for adolescents diagnosed with MTC. Therefore, this subset of patients with MTC face a substantial unmet need.[24]

Cabozantinib is additionally associated with a poor adverse event (AE) profile, leading to dose reductions in 82% of patients in the EXAM trial and 22% discontinuing treatment due to adverse events.[54, 68] As part of NICE TA742, a clinical expert experienced in the treatment of MTC stated that the significant toxicity associated with cabozantinib results in the majority of patients requiring a dose reduction within 6 months of treatment.[2, 26] With the high rate of AEs, 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.[54, 55] Furthermore, a subset of patients are not fit enough to receive first-line cabozantinib. These patients are ineligible for treatment with cabozantinib and so BSC represents their only treatment option.

There is therefore a high unmet need in the *RET*-mutant MTC population for a systemic treatment for patients who have not previously received any systemic therapy with improved efficacy and tolerability than that offered by the currently available treatments in UK clinical practice. As *RET* mutations are known to contribute to oncogenicity in MTC, the highly selective targeting of the *RET* receptor allows for a potent anti-tumour response with minimal off-target effects.[10] Selpercatinib will offer a tolerable and effective alternative to cabozantinib for systemic therapy naïve patients, that specifically targets *RET* mutations to offer a less toxic regimen. Selpercatinib also addresses the critical unmet need for those patients who are ineligible for cabozantinib, providing an effective treatment alternative to BSC.

Thyroid cancer

Thyroid cancer diagnostic pathway

As outlined in Section B.1.3.1, TC is usually diagnosed in asymptomatic patients, discovered accidentally during medical evaluations for other reasons. Thyroid nodules or neck masses are the most common primary symptom in symptomatic patients, with other symptoms including difficulty swallowing or breathing, pain or tenderness around the neck or ears, or changes 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.[56]

Similarly for MTC, ultrasonography is routinely used to evaluate thyroid nodules, with the initial diagnosis of TC often made with ultrasound-guided fine needle aspiration to sample cells from the thyroid or neck lymph nodes. ATCs 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.[27]

For patients undergoing differential diagnosis, a similar process is used as for MTC, whereby evaluation of tests, including imaging studies and blood tests, will determine the histology, size, stage and extension of the tumour, which in turn will determine the appropriate treatment strategy.[27]

Thyroid cancer treatment pathway

As the long-term prognosis for patients treated for DTC is usually favourable when disease is localised,[11] the objective of initial 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.[39, 64] 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.[27] 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.[27] Patients who develop local, regional or metastatic disease (5–20% of patients) not amenable to surgery should be treated with radioactive iodine therapy.[27]

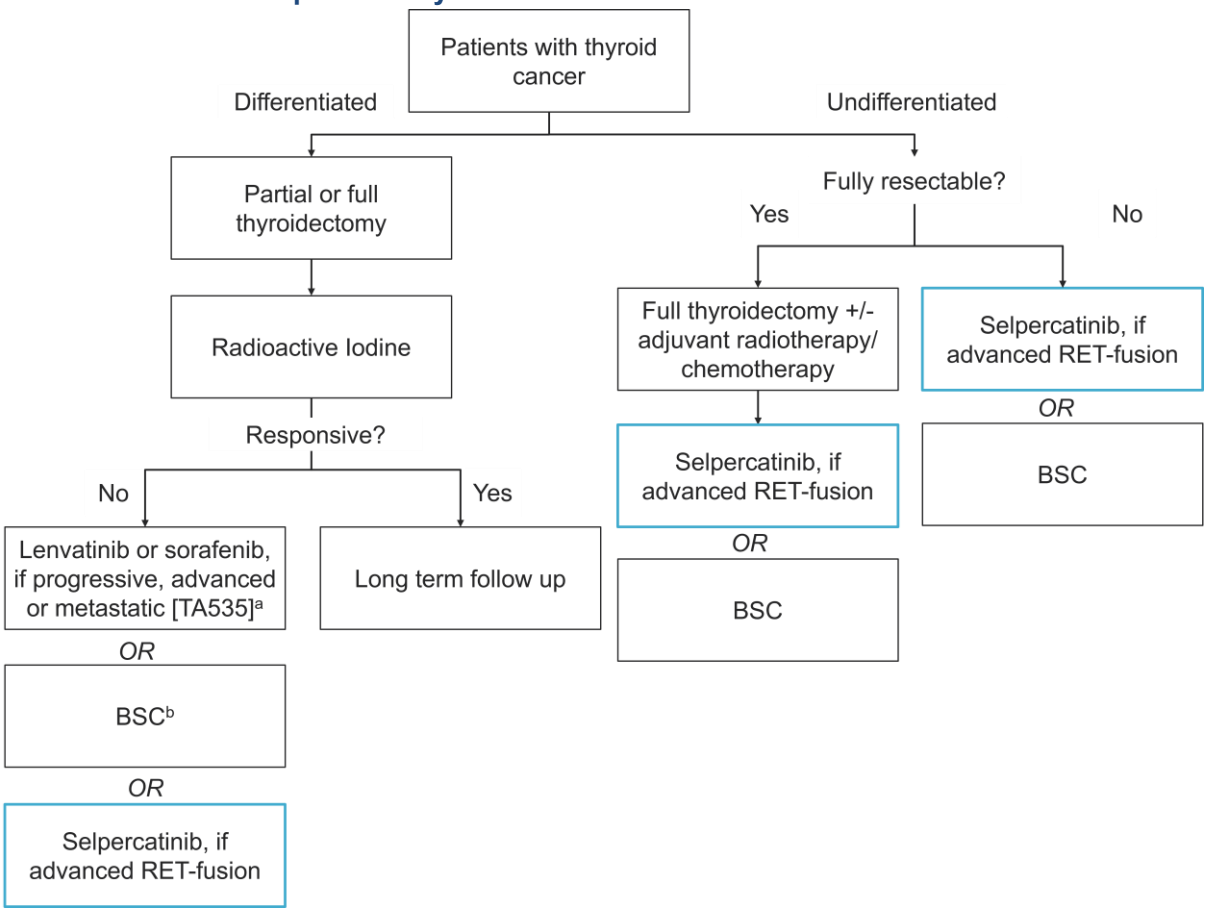
Around 5% to 15% of people with DTC develop radioactive iodine refractory DTC; this is the patient population of interest in this submission.[55] In the UK, lenvatinib and sorafenib are the only treatments recommended for adult patients with DTC classified as progressive, advanced or metastatic that was not responsive to radioactive iodine, if they are tyrosine kinase inhibitor (TKI)-naïve (TA535).[25] Based on feedback from UK clinical experts during prior NICE appraisals in TC, as well as interviews conducted to support this appraisal, lenvatinib is the dominant choice in clinical practice over sorafenib; during interviews to support this submission, UK clinical experts stated that approximately 90–95% of patients that receive an MKI currently receive lenvatinib.[3, 24] As such, sorafenib is not considered a relevant comparator for selpercatinib in this indication. At present there are no *RET*-specific treatments available for use in the UK in for those systemic therapy naïve patients experiencing iodine refractory DTC.

The long-term prognosis for ATC is considerably worse than other forms of TC, therefore total thyroidectomy may be curative for very small tumours, and in more advanced disease, surgery may be of benefit only if full resection can be achieved. External beam radiotherapy and chemotherapy may be used as adjuvant treatments in patients undergoing resection and no evidence of distant disease. When complete resection cannot be achieved, 'debulking' surgery, in which tumour mass is reduced but not totally resected, should be avoided. In selected cases, palliative chemoradiation may be of some value.[27]

In UK clinical practice, lenvatinib and sorafenib are only recommended by NICE for the treatment of DTC in adults.[25] There are no alternative options for patients with ATC or adolescent patients aged 12–17 years old with DTC, so these patients typically receive BSC.[3] Selpercatinib is currently available for adult patients who have ATC and who have had no prior treatment with a MKI, but this is only available via the CDF.[66]

The proposed treatment pathway and positioning of selpercatinib for people aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy (who have not previously received systemic therapy) is outlined in Figure 5. This treatment pathway was validated as representative of UK clinical practice by UK clinical experts interviewed to support this appraisal.[3]

Figure 5: Treatment pathway and proposed positioning of selpercatinib in patients with advanced RET fusion-positive thyroid cancer



Treatments recommended by NICE via the CDF are not represented on the above treatment pathway figure as they are not considered to be routinely available in UK clinical practice.
[a] UK clinical experts stated that approximately 90–95% of patients that receive an MKI currently receive lenvatinib, making this MKI the primary comparator in TC in UK clinical practice.[3, 24]
[b] Individuals who are ineligible for treatment with a MKI, including adolescent patients aged 12–17 years old with TC.[25, 66]
Abbreviations: ATC: anaplastic thyroid cancer; BSC: best supportive care; *RET*: rearranged during transfection; TA: technology appraisal; TC: thyroid cancer.

Unmet need in thyroid cancer

As discussed in Section B.1.3.1, the prognosis associated with advanced TC is poor with a one-year survival rate for stage IV TC of 77%.[16] The currently approved first-line MKI treatments, lenvatinib and sorafenib, demonstrate an OS of between 31.8 and 41.6 months and 23.0 and 39.4 months, respectively, for patients with RET wild-type TC.[16, 55] The poor prognosis associated with currently available treatments, as well as well-known toxicities impacting physical health, may lead to severe impacts on patient quality of life, as noted by patient experts in TA742.[2]

The currently available MKI treatments are often associated with several off-target effects, resulting in a high rate of AEs. In the SELECT trial, which assessed the efficacy of lenvatinib for treating progressive, locally advanced or metastatic DTC, AEs of grade 3 or higher were reported in 85% of patients treated with lenvatinib (n=261), compared to 30% in patients treated with placebo (n=131). Dose interruptions (82%), reductions (68%) and discontinuations (16.5%) were also considerably higher in patients treated with lenvatinib than placebo (18%, 5% and 5% respectively).[54, 68] For patients who are contraindicated to or are unlikely to tolerate the toxicity profile of MKIs, there are currently no alternative treatment options in the first line, and patients are treated palliatively with BSC.

As such, there is a high unmet need in the advanced *RET* fusion-positive TC population for an effective treatment option that is available to patients as soon as possible in the treatment pathway, who would otherwise face a poor prognosis. This unmet need is particularly high for patients who are ineligible for treatment with MKIs, such as adolescents aged 12–17 years old and patients with ATC, whose only treatment option is BSC following radioactive iodine therapy (if this therapy is appropriate). Through specific targeting of *RET*-mutations, with the potential to decrease off-target effects and AEs, and improve efficacy, selpercatinib may address the unmet need for a tolerable systemic therapy for the treatment of systemic therapy naïve *RET* fusion-positive TC.[69]

Trial data on selpercatinib indicates that it is well-tolerated, with published literature indicating that highly selective first-generation *RET* inhibitors demonstrate greater tolerability when compared to MKIs.[9, 69] This is particularly key for the subset of patients contraindicated or unable to tolerate treatment with MKIs, with selpercatinib also presenting a much needed treatment option for those patients with undifferentiated subtypes of TC who are often treated palliatively with BSC.

Positioning of selpercatinib and comparators

The proposed positioning of selpercatinib in this submission is:

- For “people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)”.
- For “people aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)”

The relevant comparators for selpercatinib for patients with advanced *RET*-mutant MTC who require systemic therapy are cabozantinib and BSC (for patients who are ineligible for cabozantinib). According to UK clinical experts during interviews conducted to support this submission, 80–90% of patients with advanced *RET*-mutant MTC receive cabozantinib, positioning cabozantinib as the primary comparator to selpercatinib in the *RET*-mutant MTC population.[3]

The relevant comparators for selpercatinib for patients with advanced *RET*-fusion positive TC who require systemic therapy are lenvatinib and BSC; based on feedback obtained from UK clinical experts during interviews conducted to support this appraisal, 80–85% of patients currently receive lenvatinib. Therefore, lenvatinib is considered the primary comparator to selpercatinib in the *RET*-fusion positive TC population.[3]

During interviews conducted to support this appraisal, UK clinical experts confirmed these represent the relevant comparators to selpercatinib in each population.[3]

Summary

A positive recommendation for the use of 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 systemic therapy naïve patients, representing a substantial improvement in care for patients with advanced *RET*-fusion positive TC and *RET*-mutant MTC.

With the highly specific and potent targeting of *RET* alterations, selpercatinib may offer an effective treatment option with reduced AEs for *RET*-altered thyroid cancer when compared to lenvatinib, and a well-tolerated and effective alternative to cabozantinib for patients with *RET*-mutant MTC. Furthermore, selpercatinib is anticipated to address the high unmet need in patients who are ineligible for currently available treatments, including due to their significant toxicity profile and adolescent patients aged 12–17 years old who are ineligible for currently available MKIs, whose only option is BSC.

B.1.4 *Equality considerations*

Females are more likely to be diagnosed with thyroid cancer, with UK data indicating that 72% of thyroid cancer cases occur in females and the remaining 28% in males.[48] Selpercatinib as a first-line therapy in thyroid cancer will continue to reduce the health inequalities for female patients with thyroid cancer.

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 is 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 need to continue improving access to these services.

B.2 Clinical effectiveness

Summary of the clinical efficacy and safety evidence for selpercatinib in *RET*-altered thyroid cancer and medullary thyroid cancer

LIBRETTO-001

- The clinical evidence base for selpercatinib in patients with *RET*-altered TC and MTC is provided by the LIBRETTO-001 trial: an ongoing, multicentre, Phase I/II, open-label study enrolling patients across multiple tumour types and lines of therapy.
    - Of relevance to the populations covered by this submission, LIBRETTO-001 includes a cohort of patients with RET-mutant MTC who were cabozantinib/vandetanib naïve (N=143) and a cohort of patients with RET-fusion positive TC who were treatment naïve (N=24).
    - Due to comparator data availability, data from the any-line MTC (N=295) and TC (N=65) patient populations are used in the ITCs and are therefore also presented in this submission.
- The LIBRETTO-001 study is aligned with the decision problem specified in the NICE scope and the patient population is reflective of patients with untreated, advanced *RET* fusion-positive TC and *RET*-mutant MTC in UK clinical practice.

Efficacy

- The primary endpoint in the LIBRETTO-001 trial was objective response rate (ORR). ORR in the cabozantinib/vandetanib naïve *RET*-mutant MTC population was 82.5% [redacted]143; 95% confidence interval [CI]: 75.3, 88.4), and in the systemic therapy naïve RET fusion-positive TC population, ORR was 95.8% [redacted]24; 95% CI: 78.9, 99.9).[70]
    - The majority of patients in the cabozantinib/vandetanib naïve *RET*-mutant MTC population experienced at least a partial response (PR) upon treatment with selpercatinib, with 58.7% of patients experiencing a PR and 23.8% of patients experiencing a complete response (CR).[70]
    - The majority of patients (75.0%) in the systemic therapy naïve RET fusion-positive TC population experienced a PR, and 20.8% patients experienced a CR, upon treatment with selpercatinib.[70]
- In the cabozantinib/vandetanib naïve *RET*-mutant MTC population, median duration of response (DOR), progression-free survival (PFS) and overall survival (OS) were [redacted], with median follow-up of 39.4 months, 42.4 months and [redacted] months, respectively.[70]
- In the systemic therapy naïve *RET* fusion-positive TC population median DOR, PFS and OS were also [redacted], with median follow-up of 17.8 months, 24.9 months, and [redacted] months, respectively.[70]
- Overall, results observed in the any-line MTC (N=295) and TC (N=65) populations were consistent with results observed in the treatment-naïve specific respective populations.

LIBRETTO-531

- Late-breaking data are available for the cabozantinib/vandetanib naïve advanced *RET*-mutant MTC population of relevance to this submission via the LIBRETTO-531 trial, a multi-centre, open-label and randomised Phase III trial investigating selpercatinib versus cabozantinib or vandetanib. Data from LIBRETTO-531 are immature but are presented for completeness.
    - High rates of response were observed in the selpercatinib treatment arm, with an ORR of 69.4% compared to 38.8% in the cabozantinib/vandetanib arm.
    - Selpercatinib was also comparatively well-tolerated, with 37.3% of patients in the treatment arm experiencing ≥Grade 3 AEs related to treatment, compared with

68.0% of patients in the cabozantinib/vandetanib arm.

Indirect treatment comparisons

- LIBRETTO-001 is a single-arm trial, and no head-to-head trials with sufficient follow up are currently available to directly compare selpercatinib versus relevant comparators in the TC and MTC indications. Therefore, indirect treatment comparisons (ITCs) were conducted to inform the relative efficacy estimates for selpercatinib in LIBRETTO-001 versus the relevant comparators for this appraisal.
    - For selpercatinib versus cabozantinib and BSC in the RET-mutant MTC population, matching adjusted indirect comparison (MAICs) were conducted.
    - For selpercatinib versus lenvatinib and BSC in the RET fusion-positive TC population, naïve ITCs were conducted.
- Overall, the ITCs conducted to generate comparative efficacy evidence for selpercatinib versus relevant comparators used the best available data and methods outlined in NICE DSU TSD 18.[71] In both the *RET*-mutant MTC and *RET* fusion-positive TC populations, selpercatinib demonstrates clinically meaningful and statistically significant treatment benefits versus the primary comparators in UK clinical practice.

Safety

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (regardless of tumour type or treatment history), with the overall safety analysis set (OSAS; N=837), the RET-mutant MTC safety analysis set (SAS; N=324) and the RET fusion-positive TC SAS (N=66) presented in this submission.[70] Data from the RET-mutant MTC safety analysis set (SAS; N=324) and the RET fusion-positive TC SAS (N=66) inform AEs in the cost-effectiveness analysis and are therefore presented in Section B.2.10.
- Permanent discontinuation of therapy due to treatment-emergent adverse events (TEAEs) related to selpercatinib were infrequent in the MTC SAS and TC SAS (5.2%, and 1.5%, respectively), with no predominant pattern among the individual AEs reported.[70]
- Grade 3 or 4 TEAEs were reported in [redacted] patients in the *RET*-mutant MTC SAS and [redacted] patients in the *RET* fusion-positive TC SAS, irrespective of relatedness to selpercatinib.
- TEAEs were easily monitored and managed through dose interruption, dose reduction or concomitant medication.

Conclusion

- The clinical effectiveness evidence from the LIBRETTO-001 trial and ITCs versus comparator trials indicate a clinically meaningful and statistically significant benefit of selpercatinib treatment for patients with untreated advanced *RET*-altered TC and MTC versus currently available treatments. Safety evidence from the LIBRETTO-001 trial also demonstrates that selpercatinib is well-tolerated.
- There are currently no *RET*-targeted therapeutic options available on the NHS for treating *RET*-altered TC and MTC for systemic therapy naïve patients. Selpercatinib offers a safer and more effective treatment option, driving a deep and durable response in patients, than currently available standard first-line treatments for *RET*-altered TC and MTC in the UK. Furthermore, selpercatinib offers an effective treatment option for those who would currently be treated palliatively with BSC.

B.2.1 *Identification and selection of relevant studies*

A *de novo* systematic literature review (SLR) was conducted in September 2019, with the most recent update conducted in May 2023, to identify all relevant clinical evidence on selpercatinib, and relevant comparators, in patients with *RET*-mutant MTC and *RET* fusion-positive TC. A total of 5,563 records were identified across the SLR searches, with 3,259 additional records identified from conference proceedings, on-going trials, and bibliographic sources. Overall, 90 records presenting data on 24 primary studies evaluating patients with thyroid cancer were included in the SLR. Of these, 15 trials included patients with *RET*-altered tumours.

Full details of the SLR, including the search strategy, study selection process and detailed results are presented in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical SLR identified one study of interest for selpercatinib in the populations of interest, LIBRETTO-001. The pivotal LIBRETTO-001 trial provides the main body of evidence for this submission, used to support the conditional marketing authorisation in the *RET*-mutant MTC indication and the anticipated marketing authorisation for the *RET* fusion-positive TC indication. LIBRETTO-001 is an ongoing, multi-centre, open-label and Phase I/II trial investigating the maximum tolerated dose (MTD), safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumour activity of selpercatinib in patients with advanced *RET*-altered solid tumours.[72] LIBRETTO-001 represents the first in-human Phase I/II trial for selpercatinib, with an overview of this trial presented in Table 3.

The eligibility criteria for the LIBRETTO-001 trial are broader than the populations of relevance for this submission, including patients ≥12 years old with locally advanced or metastatic solid tumours. Two subgroups of patients in the trial are in line with the populations of relevance for this submission:

- For “people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)”
- For “people aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)”

An ongoing Phase III trial, LIBRETTO-531, provides early-stage supporting evidence for selpercatinib in the *RET*-mutant MTC population. Brief details on LIBRETTO-531 are presented in Section B.2.6.3, B.2.10.5 and B.2.11, with further details presented in Appendix M.

Table 3: Clinical effectiveness evidence

Study	**LIBRETTO-001 (NCT03157128)[72, 73]**
Study design	A multicentre, open-label, Phase I/II study in patients with advanced solid tumours with *RET* activations, consisting of two parts: • Phase I: dose escalation and expansion • Phase II: dose expansion
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: • Who had an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2 or LPS ≥40% This submission considers patients enrolled in LIBRETTO-001 with *RET*-mutant MTC and *RET* fusion-positive TC.		
Intervention(s)	Selpercatinib, once or twice daily, depending on the dose level assignment. A recommended Phase II starting dose of 160 mg BID was selected during Phase I of LIBRETTO-001.		
Comparator(s)	NA		
Indicate if study supports application for marketing authorisation	Yes	**Indicate if study used in the economic model**	Yes
Rationale if study not used in model	NA		
Reported outcomes specified in the decision problem	**Measures of disease severity and symptom control:**[a] • Response rate (measured via ORR, DOR and BOR in the LIBRETTO-001 trial) • **PFS** • **OS** **Safety outcomes:** • **AEs of treatment** **HRQoL:** • EORTC-QLQ-C30		
All other reported outcomes	• DOR • Best overall response • Clinical benefit rate (CBR) • 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		

[a] Bolded outcomes indicate those included in the economic model.
Abbreviations: AE: adverse events; BID: twice daily; CBR: clinical benefit rate; CNS: central nervous system; DOR: duration of response; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; LPS: Lansky performance score; MTC: medullary thyroid cancer; NA: not applicable; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023)[73]

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

B.2.3.1 Trial design and methodology

LIBRETTO-001 trial design

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., NSCLC, thyroid, pancreas, colorectal), *RET*-mutant MTC and other tumours with *RET* activation. The patient population included patients with locally advanced or metastatic solid tumours, 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 aged over 18 years were eligible for the trial, with patients as young as 12 years old enrolled at countries and sites with approval from local regulatory authorities.[72, 73]

Patients were screened for eligibility based on the criteria presented in Table 6. 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 seven cohorts of patients harbouring *RET* alterations were defined and in which the efficacy and safety of selpercatinib was assessed. The study is currently in Phase II.[72, 73] A schematic of the trial is presented in Figure 6.

Patient cohorts

Based on results from Phase I of the LIBRETTO-001 trial, the safety review committee (SRC) selected a recommended Phase II dose (RP2D) of 160 mg.[74] During Phase II, patients were subsequently enrolled into one of seven 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). 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, 2 and 5, whilst *RET*-mutant MTC patients were included in Cohorts 3, 4 and 5 (Table 4).

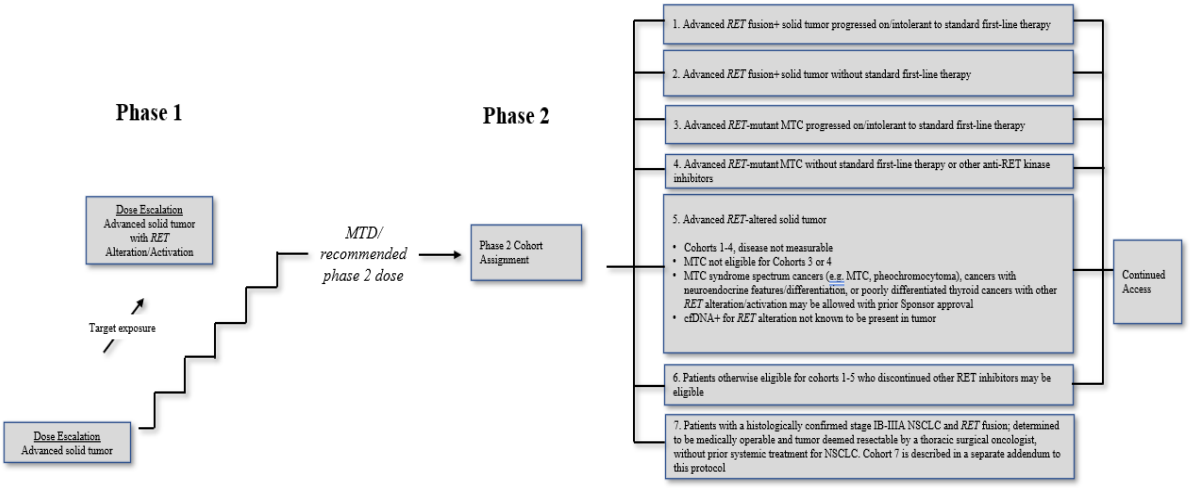
Table 4: LIBRETTO-001 patient cohorts

Patient cohort	Description
Cohort 1	Advanced *RET* fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy
Cohort 2	Advanced *RET* fusion-positive solid tumour without prior standard first-line therapy
Cohort 3	Advanced *RET*-mutant MTC progressed on or intolerant to ≥1 prior standard first line therapy
Cohort 4	Advanced *RET*-mutant MTC without prior standard first line therapy (cabozantinib or vandetanib) or other kinase inhibitors with anti-*RET* activity
Cohort 5	Advanced *RET*-altered solid tumour, including: • Patients from Cohorts 1 through 4 without measurable disease • MTC patients not meeting the requirements for Cohorts 3 or 4

	• MTC syndrome spectrum cancers, cancers with neuroendocrine features/differentiation or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval • Cell-free DNA positive for a RET gene alteration not known to be present in a tumour sample
Cohort 6	Patients otherwise eligible for cohorts 1 through 5 who discontinued other *RET* inhibitors may be eligible
Cohort 7	Patients with a histologically confirmed stage IB-IIIA NSCLC and RET fusion; determined to be medically operable and the tumour deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC.

Abbreviations: DNA: deoxyribonucleic acid; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off)[73]

Figure 6: 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 Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off)[73]

Analysis sets

As discussed in Section B.2.2, the eligibility criteria for the LIBRETTO-001 trial were 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 then categorised into broad groupings of patients with *RET* fusion-positive NSCLC, *RET*-mutant MTC, and *RET* fusion-positive thyroid cancer, as shown in Figure 7.

In line with the decision problem for this submission, clinical effectiveness evidence for selpercatinib is primarily presented for the following patient subgroups:

- People aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy), corresponding to 'MTC:Cab/Van Naïve': the cabozantinib/vandetanib naïve *RET*-mutant MTC efficacy analysis set (N=143)

- People aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy), corresponding to 'TC:TrtSysNaïve': the systemic therapy naïve *RET* fusion-positive TC efficacy analysis set (N=24)

As a single-arm trial, the clinical effectiveness and safety of selpercatinib in *RET*-altered TC and MTC versus relevant comparators in UK clinical practice could not be assessed directly in LIBRETTO-001. Thus, indirect treatment comparisons (ITCs) were conducted for the TC and MTC patient populations, as discussed in Section B.2.9. Due to data availability for the relevant comparator trials, the MTC and TC any-line populations (as shown in Figure 7) were used to derive the comparative efficacy of selpercatinib in these patient populations. The any-line MTC and TC populations were comprised of the following patient analysis sets:

- MTC any-line population (N=295): comprised of the 'MTC: Cab/Van Naïve' analysis set (N=143) and the 'MTC: Cab/Van' (cabozantinib or vandetanib experienced patients with MTC) analysis set (N=152)
- TC efficacy any-line (N=65): comprised of the 'TC: TrtSysNaïve' analysis set (N=24) and the 'TC: TrtSys' (systemic therapy experienced patients with TC) analysis set (N=41)

For completeness, clinical effectiveness results for these efficacy analysis sets are presented in this submission, in Section B.2.6.

Definitions of the key study population analysis sets, including safety analysis sets, for *RET*-mutant MTC and *RET* fusion-positive patients included in the LIBRETTO-001 trial are presented in Table 5.

Figure 7: Enrolment and derivation of analysis sets in the LIBRETTO-001 trial*

*Blue boxes indicate the efficacy analysis sets used within this submission to inform clinical effectiveness results (TC:TrtSys and MTC:Cab/Van Naïve) and ITC results (TC and MTC any-line populations). Grey boxes indicate analysis sets not relevant to the patient populations considered in this submission.
Abbreviations: BID: twice daily; cab: cabozantinib; MTC: medullary thyroid cancer; N: number of patients within category; NSCLC: non-small cell lung cancer; OSAS: overall safety analysis set; QD: once daily; *RET*: rearranged during transfection; TC: thyroid cancer; van: vandetanib.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Table 5: Analysis set definitions

Trial name	LIBRETTO-001
***RET*-mutant MTC**	
MTC any-line population N=295	All efficacy eligible[a] patients with *RET*-mutant MTC. This patient population was comprised of the MTC:Cab/VanNaïve and MTC:Cab/Van analysis sets.
MTC:Cab/VanNaïve N=143	Efficacy eligible[a] patients that have had no prior systemic therapy or have been treated with a prior systemic therapy besides cabozantinib and vandetanib. These patients were enrolled into Cohort 4 or 5
MTC:Cab/Van N=152	Efficacy eligible[a] patients previously treated with cabozantinib and/or vandetanib, enrolled into Cohort 3 or 5
***RET* fusion-positive TC**	
TC any-line population N=65	All efficacy eligible[a] patients with *RET* fusion-positive TC. This patient population was comprised of the TC:TrtSysNaïve and TC:TrtSys analysis sets.
TC:TrtSysNaïve N=24	Efficacy eligible[a] patients who have received no prior systemic therapy other than radioactive iodine, enrolled into Cohort 2 or 5
TC:TrtSys N=41	Efficacy eligible[a] patients who have previously received systemic therapy (i.e., sorafenib, lenvatinib) other than radioactive iodine, enrolled into Cohort 1 or 5
Safety set	

Overall safety analysis set (OSAS) N=837	All patients who received at least 1 or more doses of selpercatinib in LIBRETTO-001 regardless of diagnosis or line of therapy at the 13th January 2023 DCO
MTC safety analysis set N=324	All patients with *RET*-mutant MTC who received at least one dose of selpercatinib in LIBRETTO-001 at the 13th January 2023 DCO
TC safety analysis set N=66	All patients with *RET* fusion-positive TC who received at least 1 dose of selpercatinib in LIBRETTO-001 at the 13th January 2023 DCO

[a] Patients who had received at least one dose of selpercatinib and had achieved at least six months of patient follow-up time from this first dose of selpercatinib (or disease progression or death, whichever occurred first) as of 13th January 2023 were considered eligible for efficacy analyses.
Abbreviations: Cab: cabozantinib; DCO: data cut-off; MTC: medullary thyroid cancer; OSAS: overall safety analysis population; RET: rearranged during transfection; TC: thyroid cancer; van: vandetanib.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

LIBRETTO-001 trial methodology

Individual patients continued selpercatinib dosing in 28-day cycles until progressed disease (PD), unacceptable toxicity, or other reasons for treatment discontinuation.[73] 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 ORR using RECIST v1.1. Secondary oncological endpoints included DOR, PFS and OS, whilst the safety, tolerability and PK properties of selpercatinib were also considered. A summary of the methodology and trial design of LIBRETTO-001 is presented in Table 6.

Table 6: Summary of LIBRETTO-001 trial methodology

Trial name	LIBRETTO-001
Location	A total of 80 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, and 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 patients	**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 12 • ECOG performance status of 0, 1, or 2 (in patients aged ≥16 years) or LPS ≥40% (in patients aged <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 National Cancer Institute Common Terminology for Adverse Events (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, and subsequently used as the starting dose for patients in the Phase II expansion 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 IRC assessment using RECIST v1.1
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 v1.1 or RANO **Phase II** ***Efficacy*** • ORR by investigator assessment using RECIST 1.1 • Best change in tumour size from baseline, by IRC and investigator assessment • DOR by IRC and investigator assessment • CNS ORR by IRC assessment • CNS DOR by IRC assessment • Time to any and best response by IRC and investigator assessment • CBR by IRC and investigator assessment • PFS by IRC and investigator assessment • OS • Biochemical response

	Safety • Frequency, severity, and relatedness of TEAEs and SAEs, deaths and clinical laboratory abnormalities • Changes in haematology and blood chemistry values • Assessments of physical examinations • Vital signs • ECGs ***Pharmacokinetic properties of selpercatinib*** • Plasma concentrations of selpercatinib and PK parameters, including, but not limited to, $AUC_{(0-24)}$, Cmax, and Tmax **Exploratory endpoints** • Determination of the relationship between pharmacokinetics and drug effects (including efficacy and safety) • Evaluations of serum tumour markers • Carcinoembryonic antigen (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 the cabozantinib/vandetanib naïve MTC and systemic therapy naïve TC patients populations (see Table 5, Section B.2.4 for definitions of these analysis sets):
	• Age (≥65 versus <65)
	• Sex (male versus female)
	• Race (white versus other)
	• ECOG (0 versus 1–2)
	• Prior systemic therapy (number and type)
	• Metastatic disease (yes versus no)
	The primary objective, ORR, and DOR were also analysed by type of *RET* mutation and type of *RET* molecular assay used for MTC patients enrolled in the cabozantinib/vandetanib naïve population, and TC patients enrolled in the systemic therapy naive population:
	• Mutation (MTC):
	  ○ M918T
	  ○ Extracellular cysteine mutation

	○ V804M/L ○ Other • Mutation (TC): ○ CCDC6 ○ NCOA4 ○ Other • Molecular assay (MTC): ○ NGS on blood or plasma ○ NGS on tumour ○ PCR ○ FISH ○ Other • Molecular assay (TC): ○ NGS on blood or plasma ○ NGS on tumour ○ FISH ○ Other
Duration of study and follow-up	The study is ongoing, with the first patient treated on 9th May 2017. At the latest DCO (13th January 2023), the median duration of follow-up for OS was [redacted] and [redacted] for the MTC and the TC patient populations of relevance to this submission, respectively. 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; AUC(0–24): area under the concentration time curve from time 0 to 24 hours; BID: twice daily; BOR: best overall response; CBR: clinical benefit rate; CEA: carcinoembryonic antigen; cfDNA: circulating free DNA; C_{max}: maximum drug concentration; 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; FISH: fluorescence in situ Hybridisation; HRQoL: health related quality of life; IRC: independent review committee; LPS: Lansky Performance Score; LTFU: long term follow-up; MTC: medullary thyroid cancer; MTD: maximum tolerated dose; 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; RAI: radioactive iodine; RANO: Response assessment in neuro-oncology criteria; RBC: red blood cell; RECIST v1.1: response evaluation criteria in solid tumours, version 1.1; RET: rearranged during transfection; RP2D: recommended Phase II dose; SFU: safety follow-up; T_{max}: time to maximum plasma concentration.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off)[73]

B.2.3.2 Patient characteristics

A summary of patient demographics, along with other baseline characteristics, is provided below for the systemic therapy naïve *RET* fusion-positive TC efficacy analysis population (N=24) and the cabozantinib/vandetanib naïve RET-mutant MTC efficacy analysis population (N=143).

RET-mutant medullary thyroid cancer

The baseline demographics and disease characteristics of the cabozantinib/vandetanib naïve RET-mutant MTC population (N=143) and the MTC any-line population (N=295) in the LIBRETTO-001 trial are presented in Table 7. A summary of prior cancer-related treatments for the cabozantinib/vandetanib naïve MTC analysis set and the any-line MTC analysis set enrolled in the LIBRETTO-001 trial is also provided in Table 8. During interviews conducted to support this appraisal, UK clinical experts confirmed that the cabozantinib/vandetanib naïve *RET*-mutant MTC population is reflective of patients with untreated, advanced *RET*-mutant MTC in UK clinical practice.[3]

The median age of the population of patients in the efficacy analysis set was 57.0 years, with a wide range of patient ages (15–87 years). The cabozantinib/vandetanib naïve MTC population included more males (58.0%) than females (42.0%), additionally, the majority of the population were white (86.7%).[70]

For the cabozantinib/vandetanib naïve *RET*-mutant MTC population (N=143, the median time from diagnosis at the 13th January 2023 DCO was [redacted] months; the majority of patients (93.7%) presented with Stage IV disease at entry to the LIBRETTO-001 trial. Median time since diagnosis for the [redacted] patients with history of metastatic disease was [redacted] months.

The majority of the cabozantinib/vandetanib naïve MTC patient population had received no prior systemic therapy; however, 9 (6.3%) patients had previously received an MKI (not including cabozantinib or vandetanib)[70] and [redacted] of patients had received 'other' types of systemic therapy, including radioactive iodine and mammalian target of rapamycin (mTOR) inhibitors. Prior MKIs received in this analysis set were reported as sorafenib ([redacted]), lenvatinib ([redacted]) and other MKIs ([redacted]).

As shown by Table 7, baseline characteristics of the MTC any-line population were closely aligned with characteristics of the cabozantinib/vandetanib naïve MTC efficacy analysis set. Due to the difference in criteria for prior cancer treatments in the analysis sets comprising the any-line MTC population, namely, the cabozantinib/vandetanib naïve and experienced patient analysis sets, prior treatments between the two efficacy analysis sets varied, as shown in Table 8.

Table 7: Baseline demographics and disease characteristics of patients with *RET*-mutant MTC in the LIBRETTO-001 trial

Characteristic	RET-mutant MTC Cabozantinib/vandetanib naïve N=143	RET-mutant MTC Any-line population[a] N=295
Age, years		
Median	57.0	58.0

Range	15–87	15–90
Overall age group, n (%)		
12 to <45 years[b]	[redacted]	[redacted]
45 to <65 years	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]
75 to <85 years	[redacted]	[redacted]
≥85 years	[redacted]	[redacted]
Sex, n (%)		
Male	83 (58.0)	180 (61.0)
Female	60 (42.0)	115 (39.0)
Race, n (%)		
White	124 (86.7)	[redacted]
Black or African American	2 (1.4)	[redacted]
Asian	8 (5.6)	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Body weight (kg)		
n	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Height (cm)		
N	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Body mass index, kg/m^2		
N	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Baseline ECOG, n (%)		
0	69 (48.3)	111 (37.6)
1	68 (47.6)	167 (56.6)
2	6 (4.2)	17 (5.8)
Stage at entry, n (%)		
I	[redacted]	[redacted]

II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	134 (93.7)	[redacted]
Missing	[redacted]	[redacted]
Time from initial diagnosis, months		
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Investigator-reported history of metastatic disease, n (%)		
Yes	[redacted]	[redacted]
Time from diagnosis of metastatic disease, months		
N	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Presence of diarrhoea at baseline, n (%)		
Yes	[redacted]	[redacted]
Calcitonin (pg/ml)		
N	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
CEA (ng/ml)		
N	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Tumour burden (at least one measurable lesion by Investigator), n (%)		
Yes	[redacted]	[redacted]
CNS metastases at baseline, by investigator (n, %)		
Yes	[redacted]	[redacted]

[a] The MTC any-line population includes the MTC: Cab/VanNaïve and MTC: Cab/Van analysis sets. [b] [redacted] in the MTC cabozantinib/vandetanib naïve efficacy analysis set and [redacted] in the MTC any-line analysis set were less than 18 years old.
Abbreviations: Cab: cabozantinib; CEA: carcinoembryonic antigen; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; MTC: medullary thyroid cancer; N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection; Van: vandetanib.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth et al (2023)[70]

Table 8: Prior cancer-related treatments for patients with *RET*-mutant MTC in the LIBRETTO-001 trial

	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Any-line population[a] N=295**
Received prior systemic therapy, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Type of prior systemic therapy, n (%)		

MKI	9 (6.3)	[redacted]
Cabozantinib	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]
Other MKIs	[redacted]	[redacted]
Other	[redacted]	[redacted]
Radioactive iodine	[redacted]	[redacted]
mTOR inhibitor	[redacted]	[redacted]
VEGF/VEGFR inhibitor	[redacted]	[redacted]
Selective *RET* inhibitor	[redacted]	[redacted]
Hormonal therapy	[redacted]	[redacted]
Other systemic therapy	[redacted]	[redacted]
Number of prior systemic regimens, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Prior systemic regimens		
Median	0 (0.0)	[redacted]
Range	0–2	[redacted]
Best response to last systemic treatment, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not Evaluated	[redacted]	[redacted]
Prior radiotherapy, n (%)		
Yes	[redacted]	[redacted]
Prior cancer-related surgery, n (%)		
Yes	[redacted]	[redacted]

[a] The MTC any-line population includes the MTC: Cab/VanNaïve and the MTC: Cab/Van analysis sets.
Abbreviations: Cab: cabozantinib; EGFR: epidermal growth factor receptor; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; mTOR: mammalian target of rapamycin; N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection; Van: vandetanib; VEGF/VEGFR: vascular endothelial growth factor/Vascular endothelial growth factor receptor.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth et al (2023)[70]

RET fusion-positive thyroid cancer

The baseline demographics and the disease characteristics of the systemic therapy naïve patients with *RET* fusion-positive TC (N=24) and the any-line patients with RET fusion-positive TC (N=65) enrolled in the LIBRETTO-001 trial are presented in Table 9 and Table 10. Prior cancer-related treatments in these populations are also presented in Table 11. During interviews conducted to support this appraisal, UK clinical experts confirmed that the systemic therapy

naïve *RET* fusion-positive TC population is reflective of patients with untreated, advanced *RET* fusion-positive TC in UK clinical practice.[3]

Overall, 24 patients in the RET fusion-positive TC population were eligible for inclusion in the systemic therapy naïve efficacy set. Importantly, these patients had received no prior systemic therapy other than radioactive iodine, for which multiple rounds of therapy were classed as distinct regimens. The systemic therapy naïve TC patient population included two different thyroid histological subtypes; the majority of patients were diagnosed with papillary TC [redacted], with [redacted] case of poorly differentiated TC [redacted]. [redacted].

Median age for the systemic therapy naïve TC population was 60.5 years, also featuring a wide range of 20–84 years. There were more males (58.3%) than females (41.7%) in the patient population; the majority of patients (75.0%) were white.[70]

The median time from initial diagnosis was [redacted] months for the systemic therapy naïve TC population. All patients had metastatic disease at enrolment, with a median time since diagnosis of metastatic disease of [redacted] months. All patients had Stage IV disease at entry to the study. Of the systemic therapy naïve TC patients, 18 out of 24 (75.0%) had received radioactive iodine as a prior therapy. By definition, patients received no other systemic therapy.

Baseline demographic characteristics were broadly aligned between the any-line TC population and the systemic therapy naïve TC population. Due to the differences in criteria between the systemic therapy naïve TC population and any-line TC population, the prior treatments received by patients varied by analysis set as shown by Table 11.

Table 9: Baseline demographics of patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

Characteristic	RET fusion-positive TC Systemic therapy naïve[a] N=24	RET fusion-positive TC Any-line population N=65
Age, years		
Median	60.5	59.0
Range	20–84	20–88
Overall age group, n (%)		
18 to <45 years	[redacted]	[redacted]
45 to <65 years	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]
75 to <85 years	[redacted]	[redacted]
≥85 years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	32 (49.2)
Female	[redacted]	33 (50.8)
Race, n (%)		
White	18 (75.0)	[redacted]
Black	0	[redacted]

Asian	1 (4.2)	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Body weight (kg)		
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Height (cm)		
n	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Body mass index, kg/m^2		
n	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Baseline ECOG, n (%)		
0	14 (58.3)	25 (38.5)
1	9 (37.5)	36 (55.4)
2	1 (4.2)	4 (6.2)
Smoking history, n (%)		
Never smoked	[redacted]	[redacted]
Former smoker	[redacted]	[redacted]
Current smoker	[redacted]	[redacted]
Missing	[redacted]	[redacted]

[a] The systemic therapy naïve *RET* fusion-positive TC analysis set includes patients who had not previously received systemic therapy, other than radioactive iodine.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth et al (2023)[70], Raez et al (2023)[75]

Table 10: Disease characteristics of patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

Characteristic	RET fusion-positive TC Systemic therapy naïve[a] N=24	RET fusion-positive TC Any-line population N=65
Primary tumour type, n (%)		
Papillary thyroid	[redacted]	[redacted]
Poorly differentiated thyroid	[redacted]	[redacted]
Anaplastic thyroid	[redacted]	[redacted]
Hürthle cell thyroid	[redacted]	[redacted]

Stage at entry, n (%)		
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	24 (100.0)	[redacted]
Missing	[redacted]	[redacted]
Time from initial diagnosis, months		
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Investigator-reported history of metastatic disease, n (%)		
Yes	[redacted]	[redacted]
Time from diagnosis of metastatic disease, months		
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
At least 1 measurable lesion by investigator, n (%)		
Yes	[redacted]	[redacted]
Sum of diameters at baseline by investigator, mm		
n	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
CNS metastases at baseline by investigator, n (%)		
Yes	[redacted]	[redacted]

[a] The systemic therapy naïve *RET* fusion-positive TC analysis set includes patients who had not previously received systemic therapy, other than radioactive iodine.
Abbreviations: CNS: central nervous system; N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth et al (2023).[70]

Table 11: Prior cancer-related treatments for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	RET fusion-positive TC Systemic therapy naïve[a] N=24	RET fusion-positive TC Any-line population N=65
Received prior systemic therapy, n (%)		
Yes	[redacted]	[redacted]
Type of prior systemic therapy, n (%)		
MKI	0 (0.0)	[redacted]
Cabozantinib	0 (0.0)	[redacted]
Vandetanib	0 (0.0)	[redacted]
Sorafenib	0 (0.0)	[redacted]
Lenvatinib	0 (0.0)	[redacted]
Other MKIs	0 (0.0)	[redacted]
Chemotherapy	[redacted]	[redacted]
Platinum	[redacted]	[redacted]

Taxane	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Other	[redacted]	[redacted]
mTOR inhibitor	[redacted]	[redacted]
EGFR inhibitor	[redacted]	[redacted]
Radioactive iodine therapy	18 (75.0)	[redacted]
Other systemic therapy	[redacted]	[redacted]
Number of prior systemic regimens, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Prior systemic regimens		
Median	1.0	[redacted]
Range	0–5	[redacted]
Best response to last systemic treatment, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not Evaluated	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Prior radiotherapy, n (%)		
Yes	[redacted]	[redacted]
Prior cancer-related surgery, n (%)		
Yes	[redacted]	[redacted]

[a] The systemic therapy naïve *RET* fusion-positive TC analysis set includes patients who had not previously received systemic therapy, other than radioactive iodine.
Abbreviations: EGFR: Epidermal growth factor receptor**;** MKI: multi-kinase inhibitor; mTOR: mammalian target of rapamycin; N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth el al (2023).[70]

B.2.3.3 *RET* testing

For patients being enrolled into a specific Phase II dose expansion cohort, evidence of a *RET* gene alteration in tumour (i.e., not just blood), as defined in Table 12, was required. However, a positive germline DNA test for a *RET* gene mutation as defined in Table 12 was acceptable in the absence of tumour tissue testing for patients with MTC.

RET mutation status and other oncogenic mutation types for the both the cabozantinib/vandetanib naïve and the any-line MTC population, as of the 13th January 2023 DCO, are summarised in Table 13. Furthermore, *RET* fusion status and other oncogenic fusion types for both the systemic therapy naïve and the any-line TC patient populations are provided in Table 14.

The most common *RET* alteration in the cabozantinib/vandetanib naïve MTC population was the M918T mutation, occurring in 86 (60.1%) patients. Similarly, this was also the most common mutation observed in the any-line MTC population (in [redacted] of patients). In the cabozantinib/vandetanib naïve MTC population, the most frequently used assay to detect *RET* alterations was NGS on tumour, used for [redacted] patients. Other reported assays included NGS on blood or plasma and polymerase chain reaction (PCR) on tumour, with a similar distribution in assays observed for the any-line MTC population.

The most common *RET* alteration in the systemic therapy naïve TC population was the CCDC6 fusion, occurring in 15 (62.5%) of patients. Similarly, this was the most frequently observed mutation in the any-line TC analysis set (in [redacted] of patients). The most frequently used assay to detect *RET* alterations in this patient populations NGS on tumour, in [redacted] patients. NGS on blood or plasma and FISH testing were other reported types of assay used, with similar trends observed for the any-line TC population.

Table 12: Definition of *RET* alterations in LIBRETTO-001

***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.

Table 13: *RET* alteration status for the Phase II cohort (MTC efficacy analysis sets, 13th January 2023 DCO)

Status	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Efficacy analysis set[a]** [redacted]
RET mutation type, n (%)		
M918T	86 (60.1)	[redacted]
V804 M/L	6 (4.2)	[redacted]
Extracellular Cysteine Mutation	34 (23.8)	[redacted]
Other	17 (11.9)	[redacted]
***RET* alteration, type of assay (n, %)**		
NGS on tumour	[redacted]	[redacted]
NGS on blood or plasma	[redacted]	[redacted]

PCR on tumour	[redacted]	[redacted]
Other	[redacted]	[redacted]

[a] *RET* alteration status data were unavailable for the N=295 any-line cohort so are presented for the N=[redacted] cohort, which also includes [redacted] patients with NMD.
Abbreviations: Cab: cabozantinib; DCO: data cut-off; PCR: polymerase chain reaction; MTC: medullary thyroid cancer; N: number of patients in efficacy analysis set; n: number of patients; NA: not applicable; NGS: next generation sequencing; NMD: non-measurable disease; NR: not reported; RET: rearranged during transfection; Van: vandetanib.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth el al (2023).[70]

Table 14: RET alteration status for the Phase II cohort (TC efficacy analysis sets, 13th January 2023 DCO)

Status	RET fusion-positive TC Systemic therapy naïve N=24	RET fusion-positive TC Any-line population N=65
***RET* fusion type (n, %)**		
CCDC6	15 (62.5)	[redacted]
NCOA4	7 (29.2)	[redacted]
Other	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
***RET* alteration, type of assay (n, %)**		
NGS on tumour	[redacted]	[redacted]
NGS on blood or plasma	[redacted]	[redacted]
FISH	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; FISH: fluorescence in situ hybridisation; PCR: polymerase chain reaction; MTC: medullary thyroid cancer; N: number of patients in efficacy analysis set; n: number of patients; NA: not applicable; NGS: next generation sequencing; NR: not reported; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth el al (2023).[70]

B.2.3.4 Patient disposition

RET-mutant medullary thyroid cancer

A summary of the patient disposition of the cabozantinib/vandetanib naïve MTC efficacy analysis set and the any-line analysis set is provided in Table 15, with patient disposition across the cabozantinib/vandetanib naïve and experienced efficacy analysis sets illustrated by the CONSORT diagram in Figure 8.

Of the 143 patients in the efficacy analysis set, [redacted] were still on treatment as of the 13th January 2023 DCO. The most common reason for treatment discontinuation was [redacted], however, [redacted] patients [redacted] in the efficacy analysis set stayed on treatment post-progression as of 13th January 2023.

A higher proportion of patients in the cabozantinib/vandetanib naïve MTC had treatment ongoing at the 13th January DCO, when compared with the MTC any-line population, as shown by Table 15. However, the frequencies of reasons for treatment discontinuation and study discontinuations were aligned between the analysis sets.

Figure 8: CONSORT diagram presenting patient disposition for the RET-mutant MTC efficacy analysis sets (13th January 2023 DCO)

[a] The MTC efficacy analysis sets includes the MTC:Cab/VanNaive, the MTC:Cab/Van, and the MTC:NMD analysis sets.
Abbreviations: Cab: cabozantinib; DCO: data cut-off; MTC: medullary thyroid cancer; RET: rearranged during transfection; N: number of patients; Van: vandetanib.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Table 15: Patient disposition of cabozantinib/vandetanib naïve *RET*-mutant MTC patients in the LIBRETTO-001 trial

	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Efficacy analysis set[a]** [redacted]
Treatment ongoing, n (%)	[redacted]	[redacted]
Reason for treatment discontinuation, n (%)		
Disease progression	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Intercurrent illness compromising ability to fulfil protocol requirements	[redacted]	[redacted]
Requirement for alternative treatment per Investigator	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]
Treated post-progression, n (%)	[redacted]	[redacted]
Study status continuing, n (%)	[redacted]	[redacted]
Reason for study discontinuation, n (%)		

Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]

[a] Patient disposition data were unavailable for the N=295 any-line cohort so are presented for the N=[redacted] cohort, which also includes [redacted] patients with NMD.
Abbreviations: MTC: medullary thyroid cancer; N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

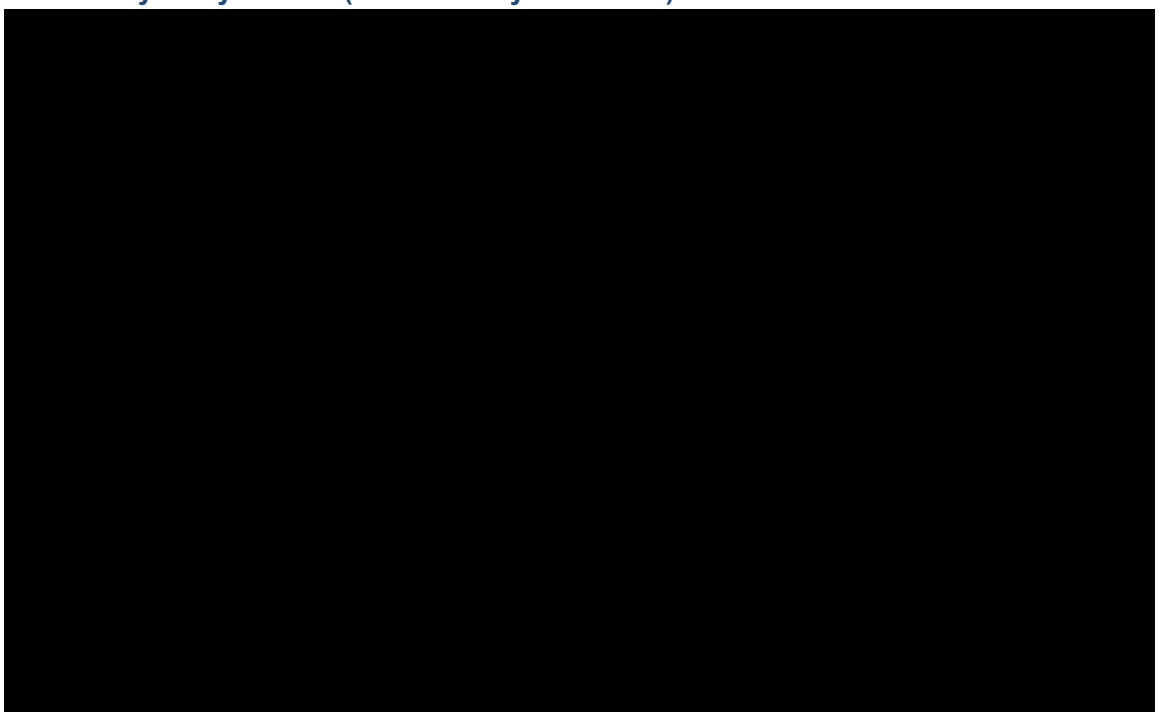
RET fusion-positive thyroid cancer

A summary of the patient disposition for the systemic therapy naïve TC efficacy analysis set and the any-line TC analysis set in the LIBRETTO-001 trial is provided in Table 16, with patient disposition across the any-line TC efficacy analysis set also illustrated in Figure 9.

Of the 24 patients in the efficacy analysis set, [redacted] were still on treatment as of the 13th January 2023 DCO. The most common reason for treatment discontinuation was withdrawal of consent. In total, [redacted] patients [redacted] in the TC efficacy analysis set remained on treatment post-progression; at the 13th January 2023 DCO, [redacted] of these [redacted] patients remained on treatment with selpercatinib. Additionally, [redacted] occurred in the analysis set.

Similarly to the trends observed between the MTC analysis sets, the systemic therapy naïve TC patient population had a higher proportion of patients with treatment ongoing at the time of the 13th January 2023 DCO when compared to the any-line TC patient population.

Figure 9: CONSORT diagram presenting patient disposition for the RET fusion-positive TC efficacy analysis sets (13th January 2023 DCO)



[a] Other solid tumours refer to patients with tissue agnostic solid tumours.
Abbreviations: DCO: data cut-off; RET: rearranged during transfection; N: number of patients; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Table 16: Patient disposition of systemic therapy naïve RET fusion-positive TC patients in the LIBRETTO-001 trial

	RET fusion-positive TC Systemic therapy naïve N=24	RET fusion-positive TC Any-line population N=65
Treatment ongoing, n (%)	[redacted]	[redacted]
Reasons for treatment discontinuation, n (%)		
Disease progression	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Intercurrent illness compromising ability to fulfil protocol requirements	[redacted]	[redacted]
Requirement for alternative treatment per Investigator	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Significant noncompliance to protocol	[redacted]	[redacted]
Other	[redacted]	[redacted]
Treated post-progression, n (%)	[redacted]	[redacted]
Study status continuing, n (%)	[redacted]	[redacted]
Reasons for study discontinuation, n (%)		
Withdrawal of consent	[redacted]	[redacted]

Death	[redacted]	[redacted]

[a] [redacted] patients continued treatment post-progression in the systemic therapy naïve TC analysis set; at the 13th January 2023 DCO, [redacted] patients were still continuing treatment.
Abbreviations: N: number of patients in efficacy analysis set; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

Analysis sets

A description of the analysis sets used in LIBRETTO-001, including a discussion on those relevant to the decision problem addressed in this submission, is provided in Section B.2.3.1.

Summary of clinical data cut-offs

The results presented in this submission are from the 13th January 2023 DCO of the LIBRETTO-001 trial, unless noted otherwise. Prior DCOs relevant to *RET*-altered MTC and TC in the LIBRETTO-001 trial include the 16th December 2019 and 15th June 2021 DCOs. For completeness, clinical efficacy and top-line safety results are presented for these DCOs in Appendix N. LIBRETTO-001 is currently ongoing, but [redacted]

Statistical methods

The statistical methods used for both the Phase I and Phase II primary analyses in the LIBRETTO-001 trial are presented in Table 17.

Table 17: 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 N • 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
	  ○ 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
	  ○ 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 DCO date
	  ○ 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)
	  ○ Censored at the date of the first dose of selpercatinib
	• Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression
	  ○ 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
	  ○ 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 DCO date
	  ○ Censored at the date of the last evaluable disease assessment

Abbreviations: AE: adverse event; CI: confidence interval; DCO: data cut-off; 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. LIBRETTO-001 CSR (13th January 2023).[73]

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of selpercatinib in the first-line setting for *RET*-altered TC and MTC patients. Definitions for these outcome measures are presented in Table 18.

Table 18. Definitions for outcome measures used in LIBRETTO-001

Outcome measure I	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. BOR was defined as the best response designations for each patient recorded between the date of the first dose of selpercatinib and the DCO, 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:[76] • **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.[77] 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 EORTC-QLQ-C30 data are presented for cabozantinib/vandetanib naïve patients with *RET*-mutant MTC and systemic therapy naïve patients with *RET* fusion-positive TC for the 13th January 2023 DCO.

Abbreviations: BOR: best overall response; CR: complete response; DCO: data cut-off; DOR: durationof 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 v1.1: Response Evaluation Criteria in Solid Tumours, version 1.1.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

B.2.5 *Critical appraisal 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	
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.[78]	
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.[79]	
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. Annals of Oncology, Volume 30, Issue Supplement_5, October 2019[80]	
Wirth, Lori & Sherman, Eric & Robinson, Bruce & Solomon, Benjamin & Kang, Hyunseok & Lorch, Jochen & Worden, Francis & Brose, Marcia & Patel, Jyoti & Leboulleux, Sophie & Godbert, Yann & Barlesi, Fabrice & Morris, John & Owonikoko, Taofeek & Tan, Daniel & Gautschi, Oliver & Weiss, Jared & De la Fouchardière, Christelle & Burkard, Mark & Cabanillas, Maria. (2020). Efficacy of Selpercatinib in *RET* -Altered Thyroid Cancers. New England Journal of Medicine. 383. 825-835. 10.1056/NEJMoa2005651.	
Manisha H. Shah, Eric Jeffrey Sherman, Bruce Robinson, Benjamin J. Solomon, Hyunseok Kang, Jochen H. Lorch, Francis P. Worden, Marcia S. Brose, Sophie Leboulleux, Yann Godbert, Marie Meurer, John C. Morris, Taofeek Kunle Owonikoko, Daniel Shao-Weng Tan, Oliver Gautschi, Jyoti D. Patel, Luxi Yang, Jennifer Kherani, Maria E. Cabanillas, and Lori J. Wirth. Selpercatinib (LOXO-292) in patients with *RET*-mutant medullary thyroid cancer.Journal of Clinical Oncology 2020 38:15_suppl, 3594-3594	
Todd M Bauer, Benjamin Besse, Herbert H F Loong, Bruce Robinson, Victoria Soldatenkova, Catherine Elizabeth Muehlenbein, Bente Frimodt-Moller and Caroline E McCoach. Safety of selpercatinib for *RET*-altered advanced solid tumours: a post hoc analysis of LIB*RET*TO-001. Cancer Res July 1 2021 (81) (13 Supplement) CT160; DOI: 10.1158/1538-7445.AM2021-CT160	
Eric Jeffrey Sherman, Lori J. Wirth, Manisha H. Shah, Maria E. Cabanillas, Bruce Robinson, Janessa J. Laskin, Matthias Kroiss, Vivek Subbiah, Alexander E. Drilon, Jennifer Wright, Victoria Soldatenkova, Pearl Plernjit French, Antoine Italiano, and Daniela Weiler. Selpercatinib efficacy and safety in patients with *RET*-altered thyroid cancer: A clinical trial update. Journal of Clinical Oncology 2021 39:15_suppl, 6073-6073	
Lori J. Wirth, Eric Jeffrey Sherman, Daniela Weiler, Maria E. Cabanillas, Bruce Robinson, Antoine Italiano, Janessa J. Laskin, Vivek Subbiah, Alexander E. Drilon, Victoria Soldatenkova, Pearl Plernjit French, Jennifer Wright, Matthias Kroiss, and Manisha H. Shah. Efficacy of selpercatinib after prior systemic therapy in patients with *RET* mutant medullary thyroid cancer. Journal of Clinical Oncology 2021 39:15_suppl, 6074-6074	
Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]	
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 selpercatinib in patients with advanced solid tumours, including *RET* fusion-positive solid tumours, MTC, and other tumours with *RET* activation. Clear, pre-specified inclusion and exclusion criteria for patients and clearly defined endpoints were used. For Part I of the study, the primary endpoint was the MTD of selpercatinib. For Part II of the study, this was ORR as assessed by IRC. Secondary endpoints are also clearly listed.
2. Was the cohort recruited in an acceptable way?	Clear and pre-specified inclusion and exclusion criteria are presented in the CSR. However, LIBRETTO-001 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. Response based endpoints, including ORR and PFS, were measured based on RECIST v1.1 criteria and assessed by an IRC. Adverse events were not assessed using common terminology criteria for adverse events (CTCAE). Neither the patients nor the outcome assessor were blinded as the trial is an open-label, single-arm study.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	NA – LIBRETTO-001 is a single-arm trial.
5B. Have they taken account of the confounding factors in the design and/or analysis?	NA – LIBRETTO-001 is a single-arm trial.
6A. Was the follow up of subjects complete enough?	Yes. Patients underwent regular assessments for response in line with the pre-specified assessment schedule.
6B. Was the follow up of subjects long enough?	Yes. Based on the 13th January 2023 data cut, median duration of follow-up for OS was [redacted] and [redacted] for the MTC and the TC patient populations of relevance to this submission, respectively. This duration of follow-up is broadly consistent with duration of follow-up observed in trials for comparator treatments in similar indications. Further follow-up would be informative to more accurately characterise long-term survival.
7. What are the results of this study?	Selpercatinib was well-tolerated and had marked antitumour activity in *RET*-altered TC and MTC and NSCLC patients, including those with resistance to prior MKIs and brain metastases from the initial results presented.

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. The results of the LIBRETTO-001 trial remain consistent across all three reported DCOs (December 2019, June 2021, January 2023) in the TC and MTC populations. IRC assessment was used to minimise bias, and increased sample sizes are available for the January 2023 DCO.
10. Can the results be applied to the local population?	Yes. These results can be applied to other TC, MTC and NSCLC patients with *RET*-altered tumours.
11. Do the results of this study fit with other available evidence?	No targeted therapy is approved for patients with *RET*-altered tumours in the first-line. However, the results of this study are aligned with preliminary data from LIBRETTO-531.
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as an effective and well-tolerated therapy for TC, MTC and NSCLC patients with *RET*-altered tumours.

Abbreviations: CT.gov: clinical trials.gov; CTCAE: common terminology criteria for adverse events; DCO: data cut-off; DOI: digital object identifier; DOR: duration of response; 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.2.6 *Clinical effectiveness results of the relevant studies*

Summary of the clinical efficacy for selpercatinib in *RET*-altered thyroid cancer

- All efficacy data presented in this section are from the most recent DCO (13th January 2023), unless otherwise stated. Results are presented for the cabozantinib/vandetanib naïve *RET*-mutant MTC population and the any-line MTC population, and the systemic therapy naïve TC analysis set and the any-line TC population.
    - In the cabozantinib/vandetanib naïve *RET*-mutant MTC population, median duration of follow-up was 39.4 months. In the systemic therapy naïve TC analysis set, median duration of follow-up was 17.8 months.

RET-mutant medullary thyroid cancer

- The primary endpoint in the LIBRETTO-001 trial, ORR, in the cabozantinib/vandetanib naïve *RET*-mutant MTC population was 82.5% [redacted]143; 95% CI: 75.3, 88.4).[70]
    - 58.7% of patients experienced a PR upon treatment with selpercatinib along with 23.8% of patients experiencing a CR, demonstrating the efficacy in targeting *RET* in this patient population.[70]
- Key secondary outcomes also assessed in LIBRETTO-001 included DOR and PFS by IRC assessment, and OS.
    - With a median follow-up of 39.4 months, median DOR was not reached (95% CI: 51.3, NE) in the cabozantinib/vandetanib naïve MTC population; disease progression was observed in [redacted] responding patients.[70]
    - With a median follow-up of 42.4 months, median PFS was not reached (95% CI: 53.1, NE) in the cabozantinib/vandetanib naïve MTC population with [redacted] events observed by IRC assessment at the DCO. [redacted] patients were alive without documented disease progression (PD) at this data-cut.[70]
    - With a median follow-up of [redacted], median OS was [redacted] for the cabozantinib/vandetanib naïve MTC population. [redacted] patients were still alive at the DCO; at ≥48 months, a survival rate of [redacted] was observed for the cabozantinib/vandetanib naïve MTC patient population.
- Efficacy outcomes for the any-line MTC population were consistent with those for the cabozantinib/vandetanib naïve MTC patient population.

RET fusion-positive thyroid cancer

- ORR in the systemic therapy naïve *RET* fusion-positive TC population was 95.8% [redacted]24; 95% CI: 78.9, 99.9), with 75.0% and 20.8% of patients experiencing PR and CR, respectively. Similarly high rates of efficacy as the cabozantinib/vandetanib naïve MTC analysis set were therefore reflected in the systemic therapy naïve TC patient population.[70]
- Key secondary outcomes for the systemic therapy naïve TC analysis set followed broadly similar trends to the cabozantinib/vandetanib naïve MTC analysis set; with a median follow-up of 17.8 months, median DOR was not reached (95% CI: 42.8, NE). Disease progression was observed in [redacted] patients.[70]
    - With a median follow-up of 24.9 months, median PFS was not reached (95% CI: 44.2, NE), with [redacted] events observed by IRC assessment at the time of the DCO. [redacted] patients were alive without documented PD at this point.[70]
    - With a median follow-up of [redacted], median OS was [redacted]. [redacted] patients were alive at the DCO, with a survival rate of [redacted] reported at ≥36 months.
- Efficacy outcomes for the any-line TC population were consistent with those for the systemic therapy naïve TC patient population.

The results presented in this submission are based on the 13th January 2023 DCO, unless noted otherwise. An overview of efficacy data from previous data cuts of LIBRETTO-001 are provided in Appendix N. For endpoints related to response and progression, the results presented in this section are based on IRC assessment. Results based on Investigator assessment are available in Appendix N.

Results from the analysis sets of relevance to the decision problem, the cabozantinib/vandetanib naïve *RET*-mutant MTC population and the systemic therapy naïve *RET* fusion-positive TC patient population, are presented in the following sections. For completeness, results for the overall TC and MTC any-line populations are also presented in this section. The any-line populations are of relevance to the ITCs required to compare the efficacy of selpercatinib to relevant comparators in UK clinical practice (Section B.2.9) and inform the cost-effectiveness analyses presented in this submission (Section B.3).

Duration of median follow-up for each endpoint for the *RET*-mutant MTC population and the *RET* fusion-positive TC population is reported in the corresponding sections. The difference in median duration of follow-up between the populations can be explained by the continued recruitment into the *RET* fusion-positive TC population whereas recruitment has closed for the *RET*-mutant MTC population.

B.2.6.1 *RET*-mutant medullary thyroid cancer

Primary endpoint: Objective response rate by RECIST v1.1

ORR was defined as the proportion of patients with best overall response (BOR) of confirmed CR or confirmed 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 DCO, 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 the cabozantinib/vandetanib naïve and the any-line MTC populations are presented in Table 20. For patients with *RET*-mutant MTC who were cabozantinib/vandetanib naïve, ORR was 82.5% [redacted]143, 95% CI: 75.3, 88.4), with 34 (23.8%) of patients achieving CR and 84 (58.7%) patients achieving PR. CBR and DCR were high in cabozantinib/vandetanib naïve patients, with rates of [redacted] and [redacted], respectively. BOR and ORR results for the any-line MTC population were consistent with the cabozantinib/vandetanib naïve MTC population.[70]

Waterfall plots illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment for the cabozantinib/vandetanib naïve and the combined overall any-line populations with *RET*-mutant MTC are shown below in Figure 10 and Figure 11, respectively, indicating that tumours were reduced by >25% for the majority of patients in both populations.

Table 20: BOR and ORR based on IRC assessment for the cabozantinib/vandetanib naïve MTC population and the any-line MTC population in the LIBRETTO-001 trial

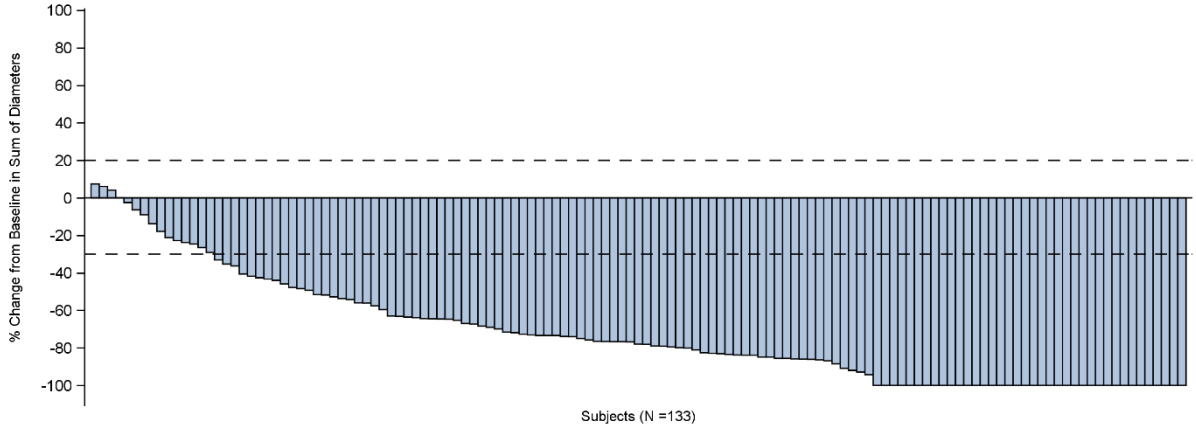
	RET-mutant MTC Cabozantinib/vandetanib naïve N=143	*RET*-mutant MTC Any-line population N=295
ORR[a]		
n (%)	[redacted](82.5)	[redacted]
95% CI	(75.3, 88.4)	[redacted]
BOR, n (%)		
CR	34 (23.8)	[redacted]
PR	84 (58.7)	[redacted]
SD	20 (14.0)	[redacted]
SD16+[b]	[redacted]	[redacted]
PD	2 (1.4)	[redacted]
Not evaluable	3 (2.1)	[redacted]
CBR (CR + PR + SD16+[b])[c]		
n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
DCR (CR + PR + SD)[d]		
N, (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

[a] Response was confirmed by a repeat assessment every ≥28 days. [b] SD16+ indicates SD lasting ≥16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. [c] Clinical benefit rate (%) is defined as the proportion of patients with best overall response of a confirmed CR, PR, or SD lasting ≥16 weeks (SD16+). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression were first met. [d] Disease Control Rate (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or SD.

Abbreviations: BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CR: complete response; disease control rate; IRC: independent review committee; MTC: medullary thyroid cancer; n: number of patients per category; N: number of patients in the population; ORR: objective response rate; PD: progressive disease; PR: partial response; RET: rearranged during transfection; SD: stable disease; SD16+: stable disease lasting 16 or more weeks.

Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[73] Wirth el al (2023).[70]

Figure 10: Waterfall plot of best change in tumour size based on IRC assessment for cabozantinib/vandetanib naïve patients with *RET*-mutant MTC



[redacted] patients are not shown, due to [redacted] patients having non-target lesions only and [redacted] patients without postbaseline target lesion measurement.
Abbreviations: IRC; independent review committee; MTC: medullary thyroid cancer; N: number of patients; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[73] Wirth et al. (2023).[70]

Figure 11: Waterfall plot of best change in tumour size based on IRC assessment for any-line patients with *RET*-mutant MTC

[redacted]

[redacted] patients are not shown, due to [redacted] patients having non target lesions only and [redacted] patients without post-baseline target lesion measurement.
Abbreviations: IRC: independent review committee; MTC: medullary thyroid cancer; N: number of patients; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).[73]

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.

DOR results for the cabozantinib/vandetanib naïve and the any-line MTC populations are summarised in Table 21. For patients with *RET*-mutant MTC who were cabozantinib/vandetanib naïve, after a median follow-up of 39.4 months, the median DOR by IRC was not reached, (95% CI: 51.3, NE). This was due to a low number of events ([redacted] observed and a high proportion of patients in the analysis set still on treatment and in response. Durable response rates in the cabozantinib/vandetanib naïve MTC analysis set were also observed; 91.4% (95% CI: 84.6, 95.3) of patients were in response for ≥12 months, reaching [redacted] at ≥48 months. DOR results for the any-line MTC population were consistent with the cabozantinib/vandetanib naïve MTC population.[70]

A Kaplan–Meier (KM) plot of DOR for the cabozantinib/vandetanib naïve MTC efficacy set is presented in Figure 12.

Table 21: DOR based on IRC assessment for the cabozantinib/vandetanib naïve MTC population and the any-line MTC population in the LIBRETTO-001 trial

	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Any-line population N=295**
Responders (n)	[redacted]	[redacted]
Reason censored (n, %)		
Alive without documented PD	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
DOR (months)		
Median	NE	[redacted]
95% CI	51.3, NE	[redacted]
Rate (%) of DOR		
≥12 months (95% CI)	91.4 (84.6, 95.3)	[redacted]
≥24 months (95% CI)	84.1 (75.9, 89.7)	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
≥60 months (95% CI)	[redacted]	[redacted]
DOR follow-up (months)		
Median	39.4	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	32.3, 45.4	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; IRC: independent review committee; MTC: medullary thyroid cancer; N: number of patients; NE: not estimable; PD: disease progression; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[73] Wirth el al (2023).[70]

Figure 12: KM plot of DOR based on IRC assessment in cabozantinib/vandetanib naïve patients with *RET*-mutant MTC

Abbreviations: DOR: duration of response; IRC: independent review committee; KM: Kaplan-Meier; MTC: medullary thyroid cancer; No.: number of patients; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).[73]

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).

An overview of the PFS results for the cabozantinib/vandetanib naïve and the any-line *RET*-mutant MTC efficacy sets are provided in Table 22. For patients with *RET*-mutant MTC who were cabozantinib/vandetanib naïve, after a median duration of follow-up of 42.4 months, median PFS was not reached (95% CI: 53.1, NE).[70]

More than half of all patients in this efficacy set [redacted] were alive without documented disease progression by IRC assessment at the DCO. The second most common reason for censoring in the cabozantinib/vandetanib naïve *RET*-mutant MTC population was subsequent anti-cancer therapy or surgery without documented PD [redacted]. Rates of PFS were high, ranging from 91.1% (95% CI: 84.8, 94.8) for ≥ 12 months, to [redacted] at ≥48 months in cabozantinib/vandetanib naïve patients. PFS results for the any-line MTC population were consistent with the cabozantinib/vandetanib naïve MTC population.[70]

KM plots of PFS for the cabozantinib/vandetanib naïve and any-line *RET*-mutant MTC analysis sets are presented in Figure 13 and Figure 14, respectively.

Table 22: PFS based on IRC assessment for the cabozantinib/vandetanib naïve MTC population and the any-line MTC population in the LIBRETTO-001 trial

	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Any-line population N=295**

Reason censored (n, %)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Duration of PFS (months)		
Median[b]	NE	[redacted]
95% CI	53.1, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥12 months or more (95% CI)	91.1 (84.8, 94.8)	[redacted]
≥24 months or more (95% CI)	82.5 (74.8, 88.0)	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]
≥48 months or more (95% CI)	[redacted]	[redacted]
Duration of follow-up (months)		
Median	42.4	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Progression status (n, %)		
Disease progression	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]
Censored	104 (72.7)	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IRC: independent review committee; MTC: medullary thyroid cancer; PD: disease progression; PFS: progression free survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth el al (2023).[70]

Figure 13: KM plot of PFS based on IRC assessment for cabozantinib/vandetanib naïve patients with *RET*-mutant MTC

Abbreviations: IRC: independent review committee; KM: Kaplan-Meier; MTC: medullary thyroid cancer; No.: number of patients; PFS: progression-free survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Figure 14: KM plot of PFS based on IRC assessment for any-line patients with *RET*-mutant MTC

Abbreviations: CI: confidence interval; IRC: independent review committee; KM: Kaplan-Meier; MTC: medullary thyroid cancer; NE: not evaluable; PFS: progression-free survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

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 DCO date were right-censored. The censoring date was determined from the date the patient was last known to be alive.

OS results for the cabozantinib/vandetanib naïve and the any-line *RET*-mutant MTC efficacy sets are summarised in Table 23. For patients with *RET*-mutant MTC who were cabozantinib/vandetanib naïve, after a median duration of follow-up of [redacted], median OS was [redacted]. The rate of OS was also high for the cabozantinib/vandetanib naïve population; survival rate at ≥36 months and ≥48 months was [redacted] and [redacted]. OS results for the any-line MTC population were consistent with the cabozantinib/vandetanib naïve MTC population.

KM plots of OS for the cabozantinib/vandetanib naïve and combined any-line patients with *RET*-mutant MTC are shown in Figure 15 and Figure 16, respectively, with Figure 15 demonstrating that the majority of patients in the cabozantinib/vandetanib naïve population were alive at the 13th January 2023 DCO.

Table 23: OS for the cabozantinib/vandetanib naïve MTC population and the any-line MTC population in the LIBRETTO-001 trial

	RET-mutant MTC Cabozantinib/vandetanib naïve N=143	RET-mutant MTC Any-line population N=295
Duration of overall survival (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of overall survival		
≥12 months (95% CI)	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
Duration of follow-up (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Survival status (n, %)		
Dead	[redacted]	[redacted]
Censored	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; MTC: medullary thyroid cancer; NE: not evaluable; OS: overall survival; PD: progressive disease; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Figure 15: KM plot of OS in cabozantinib/vandetanib naïve patients with *RET*-mutant MTC

Abbreviations: KM: Kaplan-Meier; MTC: medullary thyroid cancer; No.: number of patients; OS: overall survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Figure 16: KM plot of OS in any-line patients with *RET*-mutant MTC

Abbreviations: CI: confidence interval; KM: Kaplan-Meier; MTC: medullary thyroid cancer; NE; not evaluable; OS: overall survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

HRQoL data

HRQoL data are presented for the MTC population for the 13th January 2023 DCO, for which the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (Version 3.0) was applied at baseline and several scheduled follow-up visits.

EORTC-QLQ-C30

EORTC-QLQ-C30 (Version 3.0) is a well-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 the functioning scales and global health status 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.[81]

EORTC QLQ-C30 subscale scores (symptom and single item measures) range from 0 to 100 and higher scores represent a higher level of symptoms, therefore a worse health state.[81] Descriptive analyses reported median/quartile, mean/standard deviation (SD), and mean change/standard error (SE) from baseline for each subscale at each study visit. Patients with "improvement" in subscale scores were defined as those who demonstrated a ≥10-point change from their baseline score, as per published work in oncology.[82] Patients with "worsening" subscale scores 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.

Paper EORTC-QLQ-C30 questionnaires were provided to patients with *RET*-mutant MTC and RET fusion-positive TC. As of the 13th January 2023 DCO, EORTC-QLQ-C30 data were available for [redacted] cabozantinib/vandetanib naïve patients with *RET*-mutant MTC. To be eligible for the EORTC-QLQ-C30 analysis presented in this submission, treated patients were required to have a baseline assessment and at least one post-baseline assessment for the complete EORTC QLQ-C30 questionnaire, including all subscales.

The mean baseline score global health status/QoL subscale was [redacted] (SD=[redacted]) for eligible cabozantinib/vandetanib naïve patients with *RET*-mutant MTC. The mean baseline score for physical, emotional, cognitive, social and role function subscales were each [redacted] points.[73] The proportion of patients with any clinically meaningful improvement or worsening in the global health status or any subscales by treatment cycle are presented in Table 25. Of the [redacted] patients, [redacted] of patients experienced definite improvement in the global health status/QoL subscale on Day 1 of treatment Cycle 3. On Day 1 of treatment Cycle 9, [redacted] of patients had experienced a definite improvement. Symptom subscales of the EORTC-QLQ-C30 (Table 24) indicate a substantial proportion of patients experienced definite improvement in the diarrhoea ([redacted]) and fatigue ([redacted]) subscales.

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 Table 25 by cycle of treatment. Data are presented for Cycle three, five, seven and nine, where the largest number of patients completed the questionnaire.

Table 24: Baseline scores of the symptom subscales of the EORTC-QLQ-C30 and proportion showing improvement/worsening in *RET*-mutant MTC patients Day 1 of of Cycle 9

Subscale	*RET*-mutant MTC ([redacted])[a]		
	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]

Data presented for the cabozantinib/vandetanib naïve MTC population.
[a] Number of treated patients with available baseline and at least one post-baseline assessment for the complete EORTC QLQ-C30 questionnaire (i.e. for all EORTC scales, not per single scale).
Abbreviations: MTC: medullary thyroid cancer; RET: rearranged during transfection; SD: standard deviation.
Source: Eli Lilly Data on File (13th January 2023 data cut-off)[73]

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])[a]			
		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. Data presented for the cabozantinib/vandetanib naïve MTC population. [a] Number of treated patients with available baseline and at least one post-baseline assessment for the complete EORTC QLQ-C30 questionnaire (i.e. for all EORTC scales, not per single scale).
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 (13th January 2023 data cut-off)[73]

Bowel diaries

Due to the association of MTC with additional debilitating symptoms, including severe diarrhoea, as described in Section B.1.3.1, 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 of treatment, and on Day 1 of each cycle thereafter. An overview of the mSTIDAT data from the January 2023 DCO for patients with *RET*-mutant MTC are presented in Appendix N.

B.2.6.2 *RET*-fusion positive thyroid cancer

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

Results for IRC-assessed BOR and ORR for the systemic therapy naïve *RET*-fusion positive TC efficacy analysis set and the any-line TC analysis set are presented in Table 26. For patients with advanced *RET*-fusion positive TC who were systemic therapy naïve, ORR was 95.8% [redacted]24, 95% CI: 78.9, 99.9), with 5 (20.8%) patients experiencing a CR and 18 (75.0%) patients experiencing a PR. CBR and DCR were both high in the systemic therapy naïve *RET* fusion positive TC analysis set, both with rates of [redacted]. BOR and ORR results were similar in the any-line TC patient population compared to the systemic therapy naïve population.[70]

A waterfall plot illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment is also shown below in Figure 17, indicating that the sum of diameters of tumours were reduced >25% in [redacted]. A waterfall plot illustrating this outcome is also provided for the any-line TC patient population in Figure 18.

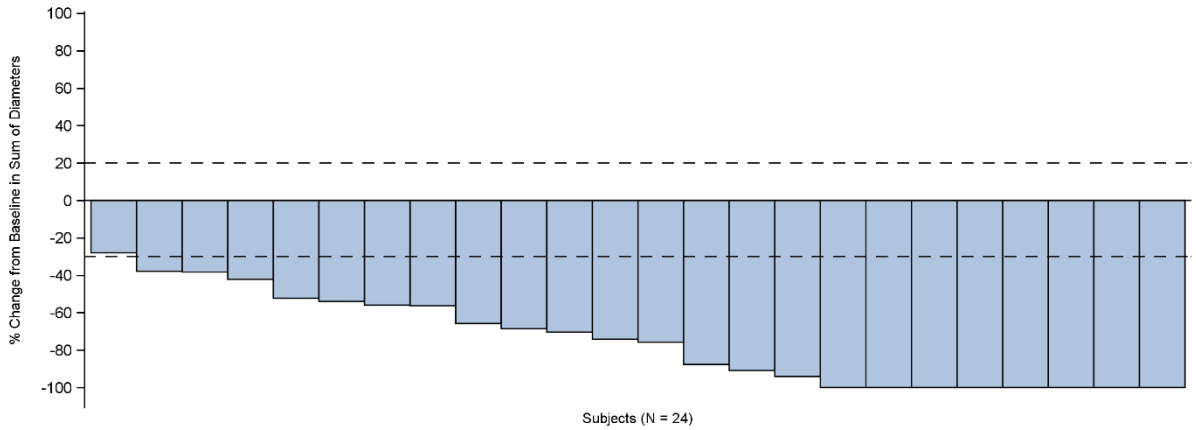
Table 26: BOR and ORR based on IRC assessment for patients with *RET*-fusion positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC Systemic therapy naïve N=24**	***RET* fusion-positive TC Any-line Population N=65**
ORR[a]		
n (%)	[redacted](95.8)	[redacted]
95% CI	78.9, 99.9	[redacted]
BOR, n (%)		
CR	5 (20.8)	[redacted]
PR	18 (75.0)	[redacted]
SD	1 (4.2)	[redacted]
SD16+b	[redacted]	[redacted]
PD	0 (0.0)	[redacted]
Not evaluable	0 (0.0)	[redacted]
CBR (CR + PR + SD16+[b])[c]		
n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
DCR (CR + PR + SD)[d]		
N, (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

[a] Response was confirmed by a repeat assessment every ≥28 days. [b] SD16+ indicates SD lasting ≥16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. [c] CBR (%) is defined as the proportion of patients with BOR of a confirmed CR, PR, or SD lasting ≥16 weeks (SD16+). SD was measured from the date of the first dose of selpercatinib until the criteria for disease progression were first met.[d] DCR (%) is defined as the proportion of patients with best overall response of confirmed CR, PR, or SD.

Abbreviations: BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DCR: disease control rate; IRC: independent review committee; n: number of patients per category; N: number of patients in the population; ORR: objective response rate; PD: progressive disease; PR: partial response; RET: rearranged during transfection; SD: stable disease; SD16+: stable disease lasting 16 or more weeks; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[73] Wirth el al (2023).[70]

Figure 17: Waterfall plot of best change in tumour size based on IRC assessment for systemic therapy naïve patients with *RET* fusion-positive TC



Abbreviations: IRC: Independent Review Committee; N: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[73] Wirth el al (2023).[70]

Figure 18: Waterfall plot of best change in tumour size based on IRC assessment for any-line patients with *RET* fusion-positive TC

Abbreviations: IRC: Independent Review Committee; N: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).[73]

Duration of response

DOR results for the systemic therapy naïve TC analysis set and the any-line TC analysis set are summarised in Table 27. After a median follow up of 17.8 months, the median DOR by IRC was not reached (95% CI: 42.8, NE), due to small patient numbers and a low number of events [redacted] observed, thus, a large proportion of patients in the efficacy set remaining on treatment and in response at the 13th January 2023 DCO. Durable response rates in the systemic therapy naïve TC analysis set were observed with 100.0% (95% CI: NE, NE) of patients in response for ≥12

months and [redacted] at ≥36 months. Rates of DOR over 48 and 60 months were [redacted].[70]

DOR results were similar in the any-line TC patient population compared to the systemic therapy naïve population, with median DOR also [redacted] (95% CI: [redacted]) and similar rates of DOR.

A KM plot of DOR for the systemic therapy naïve TC analysis set is presented in Figure 19, demonstrating similar response rates as the larger cabozantinib/vandetanib naïve MTC analysis set up to 42 months. For completeness, a KM plot of DOR for the any-line TC population is provided in Figure 20.

Table 27: DOR based on IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC Systemic therapy naïve N=24**	***RET* fusion-positive TC Any-line Population N=65**
Responders (n)	[redacted]	[redacted]
Reason censored (n, %)		
Alive without documented PD	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]
DOR (months)		
Median	NE	[redacted]
95% CI	42.8, NE	[redacted]
Rate (%) of DOR		
≥12 months (95% CI)	100.0 (NE, NE)	[redacted]
≥24 months (95% CI)	90.9 (50.8, 98.7)	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
DOR follow-up (months)		
Median	17.8	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	9.2, 42.3	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; IRC: independent review committee; N: number of patients; NE: not estimable; PD: disease progression; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[73] Wirth el al (2023).[70]

Figure 19: KM plot of DOR based on IRC assessment for systemic therapy naïve patients with *RET*-fusion positive TC

Abbreviations: DOR: duration of response; IRC: independent review committee; KM: Kaplan-Meier; No.: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).[73]

Figure 20: KM plot of DOR based on IRC assessment for any-line patients with *RET*-fusion positive TC

Abbreviations: DOR: duration of response; IRC: independent review committee; KM: Kaplan-Meier; No.: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).[73]

Progression free survival

PFS results for the systemic therapy naïve TC efficacy set and any-line TC analysis set are summarised in Table 28. After a median follow-up of 24.9 months, median PFS was not reached (95% CI: 44.2, NE). The majority of patients in the efficacy set [redacted] were alive without documented disease progression by IRC assessment at the DCO, with [redacted] events observed. Rates of PFS were high, ranging from 95.2 (70.7, 99.3) for ≥12 months, to [redacted]

[redacted] at ≥48 months, reflecting the PFS rates observed in the larger *RET*-mutant MTC analysis set.[70]

PFS results were similar in the any-line TC patient population compared to the systemic therapy naïve population, with median PFS also [redacted] (95% CI: [redacted] and similar landmark rates of PFS.

KM plots of PFS for the systemic therapy naïve TC and the any-line TC analysis sets are presented in Figure 21 and Figure 22, respectively.

Table 28: PFS based on IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC Systemic therapy naïve N=24**	***RET* fusion-positive TC Any-line population N=65**
Reason censored (n, %)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Duration of PFS (months)		
Median[b]	NE	[redacted]
95% CI	44.2, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥12 months or more (95% CI)	95.2 (70.7, 99.3)	[redacted]
≥24 months or more (95% CI)	95.2 (70.7, 99.3)	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]
Duration of follow-up (months)		
Median	24.9	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Progression status (n, %)		
Disease progression	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]
Censored	21 (87.5)	[redacted]

'*' denotes where some data have been censored.

Abbreviations: CI: confidence interval; IRC: independent review committee; PD: disease progression; PFS: progression free survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth el al (2023).[70]

Figure 21: KM plot of PFS based on IRC assessment for systemic therapy naïve patients with *RET* fusion-positive TC

Abbreviations: IRC: independent review committee; KM: Kaplan-Meier; No.: number of patients; PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Figure 22: KM plot of PFS based on IRC assessment for any-line patients with *RET* fusion-positive TC

Abbreviations: IRC: independent review committee; KM: Kaplan-Meier; No.: number of patients; PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Overall survival

OS results for the systemic therapy naïve TC efficacy set and the any-line TC analysis set are summarised in Table 29. After a median follow-up of [redacted], median OS was [redacted]

[redacted], with [redacted] patients alive at the 13th January 2023 DCO. Rate of OS remained high at ≥48 months, with a survival rate of [redacted].

OS results were similar in the any-line TC patient population compared to the systemic therapy naïve population, with median OS also [redacted] and similar landmark rates of OS.

KM plots of OS for the systemic therapy naïve TC efficacy set and the any-line TC analysis set are shown in Figure 23 and Figure 24, demonstrating that the majority of patients were alive at the 13th January 2023 DCO in both analysis sets.

Table 29: OS for the patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	RET fusion-positive TC Systemic therapy naïve N=24	RET fusion-positive TC Any-line Population N=65
Duration of OS (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of OS		
≥12 months (95% CI)	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
Duration of follow-up (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Survival status (n, %)		
Dead	[redacted]	[redacted]
Censored	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not evaluable; OS: overall survival; PD: progressive disease; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Figure 23: KM plot of OS for the systemic therapy naïve patients with *RET* fusion-positive TC

Abbreviations: KM: Kaplan-Meier; No.: number of patients; OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Figure 24: KM plot of OS for any-line patients with *RET* fusion-positive TC

Abbreviations: KM: Kaplan-Meier; No.: number of patients; OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.

HRQoL data

EORTC-QLQ-C30

At the 13th January 2023 DCO, EORTC-QLQ-C30 data were available for [redacted] systemic therapy naïve patients with *RET* fusion-positive TC.

The mean baseline score global health status/QoL subscale was [redacted] (SD=[redacted]) for eligible systemic therapy naïve patients with *RET* fusion-positive TC. The mean baseline score for physical, emotional, cognitive, social and role function subscales were each [redacted] points.[73] The

proportion of patients with any clinically meaningful improvement or worsening in the global health status or any subscales by treatment cycle are presented in Table 25. Of the [redacted] eligible patients, [redacted] of patients experienced definite improvement in the global health status/QoL subscale on Day 1 of treatment Cycle 3. On Day 1 of treatment Cycle 9 [redacted] of patients had experienced a definite improvement.

QLQ-C30 subscale scores and proportion improving/worsening

A summary of the baseline QLQ-C30 symptom subscale scores for patients with *RET* fusion-positive TC and the proportion of patients showing improvement or worsening in scores can be found in Table 30 and Table 31 by cycle of treatment. Data are presented for Cycle three, five, seven and nine.

Table 30: Baseline scores of the symptom subscales of the EORTC-QLQ-C30 and proportion showing improvement/worsening in *RET* fusion-positive TC patients at Day 1 of Cycle 9

Subscale	*RET* fusion-positive TC ([redacted])[a]		
	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]

Data presented for the systemic therapy naïve TC population.
[a] Number of treated patients with available baseline and at least one post-baseline assessment for the complete EORTC QLQ-C30 questionnaire (i.e. for all EORTC scales, not per single scale).
Abbreviations: RET: rearranged during transfection; SD: standard deviation; TC: thyroid cancer.
Source: Eli Lilly Data on File (13th January 2023 data cut-off)[73]

Table 31: Proportion of patients with *RET* fusion-positive TC with improved or worsened EORTC-QLQ-C30 compared with baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		*RET*-mutant MTC ([redacted])[a]			
		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. Data presented for the systemic therapy naïve TC population. [a] Number of treated patients with available baseline and at least one post-baseline assessment for the complete EORTC QLQ-C30 questionnaire (i.e. for all EORTC scales, not per single scale).

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 (13th January 2023 data cut-off)[73]

B.2.6.3 LIBRETTO-531

Overview of clinical effectiveness evidence

In addition to LIBRETTO-001, an ongoing Phase III trial, LIBRETTO-531, provides early-stage supporting evidence for selpercatinib in the *RET*-mutant MTC population. Further details on LIBRETTO-531 are presented in Appendix M.

An overview of the clinical efficacy results from selpercatinib and cabozantinib/vandetanib from LIBRETTO-531 are presented in Table 32. Although the data remain immature, results from LIBRETTO-531 show high rates of response in the selpercatinib treatment arm, with an ORR of [redacted]% compared to [redacted]% in the cabozantinib/vandetanib arm. In the selpercatinib arm, with a median follow-up of [redacted] months, median PFS is not estimable; in contrast, after a median follow-up of [redacted] months, median PFS in the cabozantinib/vandetanib arm is [redacted] months (95% CI: [redacted]). These results demonstrate highly promising comparative efficacy for selpercatinib versus cabozantinib/vandetanib.

Table 32: Summary of clinical efficacy results for LIBRETTO-531

Outcome	Selpercatinib N=193	Cabozantinib/vandetanib N=98
ORR (IRC)[a]		
n (%); [95% CI]	134 (69.4); [62.4, 75.8]	38 (38.8); [29.1, 49.2]
CR (IRC)		
n (%); [95% CI]	23 (11.9); [redacted]	4 (4.1); [redacted]
PR (IRC)		
n (%); [95% CI]	111 (57.5); [redacted]	34 (34.7); [redacted]
PFS (months; IRC)		
Number of events, n (%)	26 (13.5)	33 (33.7)
Disease progression, n (%)	[redacted]	[redacted]
Died (no disease progression beforehand), n (%)	[redacted]	[redacted]
Median (95% CI)[b]	NE (NE, NE)	16.76 (12.22, 25.10)
Minimum, maximum	[redacted]	[redacted]
Hazard ratio (95% CI)	0.28 (0.16, 0.48)	
Rate of PFS (%)		
≥12 months or more (95% CI)	86.8 (79.8, 91.6)	65.7 (51.9, 76.4)
≥18 months or more (95% CI)	[redacted]	[redacted]
≥24 months or more (95% CI)	76.4 (66.5, 83.8)	37.2 (21.9, 52.6)
OS (months)		
Number of events, n (%)	8 (4.1)	10 (10.2)
Number of censored, n (%)	[redacted]	[redacted]
Number alive, n (%)	183 (94.8)	84 (85.7)

Median (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
Rate of OS (%)		
≥12 months or more (95% CI)	[redacted]	[redacted]
≥18 months or more (95% CI)	95.5 (90.1, 98.0)	92.8 (83.0, 97.1)
≥24 months or more (95% CI)	[redacted]	[redacted]

'*' denotes where some data have been censored. [a] Response was confirmed by a repeat assessment every ≥28 days.
Abbreviations: CI: confidence interval; CR: complete response; IRC: independent review committee; DOR: duration of response; N: number of patients in efficacy analysis set; n: number of patients experiencing event; ORR: objective response rate; OS; overall survival; PFS: progression free survival; PR: partial response;
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73] Hadoux *et al.* (2023).[83]

B.2.7 *Subgroup analysis*

Response rate and DOR, using IRC assessment, were analysed by several demographic variables, type of RET mutation, type of molecular assay used, and types of prior therapy in the both the cabozantinib/vandetanib naïve *RET*-mutant MTC and systemic therapy naïve *RET* fusion-positive TC analysis sets, to identify any differences in the efficacy of selpercatinib in these subgroups.

B.2.7.1 *RET*-mutant medullary thyroid cancer

Subgroup analysis by demographic variables

ORR and DOR by demographics for the cabozantinib/vandetanib naïve *RET*-mutant MTC efficacy analysis set is presented in Table 33. ORR did not vary by demographic, and for the majority of results, DOR was [redacted].

Table 33: ORR and DOR by demographics based on IRC assessment for the cabozantinib/vandetanib naïve *RET*-mutant MTC analysis set

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (95% CI)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Age				
<65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
0	[redacted]	[redacted]	[redacted]	[redacted]

1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
Any metastatic disease				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; IRC: independent review committee; MTC: medullary thyroid cancer; NE: not estimable; NR: not reached; ORR: objective response rate; PR: partial response; RET: rearranged during transfection.
Sources: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Subgroup analysis by *RET* mutation

Results of the subgroup analysis of ORR and DOR by type of *RET* mutation are presented in Table 34. ORR was consistent for patients with different RET mutations. In patients with a V804M or V804L mutation, ORR was slightly lower, potentially due to small patient numbers. Median DOR by mutation type was [redacted].

The ORR and DOR by type of molecular test are also presented in Table 34. ORR was broadly consistent across all subgroups, and the median DOR for all subsets was [redacted], with the exception of patients with the NGS on blood or plasma for which DOR was [redacted] [redacted].

Table 34: ORR and DOR based on IRC assessment by *RET* mutation type and type of molecular assay for cabozantinib/vandetanib naïve patients with *RET*-mutant MTC

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
***RET* mutation type**				
M918T	[redacted]	[redacted]	[redacted]	[redacted]
Extracellular Cysteine Mutation	[redacted]	[redacted]	[redacted]	[redacted]
V804M/L[a]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[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]
FISH	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation.
Abbreviations: DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence in situ hybridisation; IRC: independent review committee; MTC: medullary thyroid cancer; NA: not applicable; NE: not estimable; NR: not reached; ORR: objective response rate; PCR: polymerase chain reaction; PR: partial response; RET: rearranged during transfection.
Sources: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Subgroup analysis by number and type of prior therapy

ORR and DOR by number of prior therapy or type of prior therapy are presented in Table 35. ORR was broadly consistent across all subgroups and the median DOR for the majority of subsets was [redacted].

Table 35: ORR and DOR by number and type of prior therapy based on IRC assessment for the cabozantinib/vandetanib naïve *RET*-mutant MTC analysis set

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior therapies				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Type of prior systemic therapy				
Prior MKI other than cabozantinib or vandetanib	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapies other than MKI	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: DOR: duration of response; IRC: Independent Review Committee; MTC; medullary thyroid cancer; NA: not applicable; NE: not estimable; NR: not reached; ORR: objective response rate; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Forest plot summary for ORR analyses

All ORR subgroup analyses performed for the cabozantinib/vandetanib naïve *RET*-mutant MTC analysis set are also summarised in Figure 25.

Figure 25: Forest plot of ORR in subgroup populations based on IRC assessment for cabozantinib/vandetanib naïve patients with *RET*-mutant MTC

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IRC: independent review committee; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; NGS: next generation sequencing; ORR: overall response rate; PCR: polymerase chain reaction; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

B.2.7.2 RET fusion-positive thyroid cancer

Subgroup analysis by demographic variables

ORR and DOR by demographics for the systemic therapy naïve TC analysis set is presented in Table 36. ORR was consistent across demographics, and for the majority of results, median DOR was [redacted].

Table 36: ORR and DOR by demographics based on IRC assessment for the systemic therapy naïve *RET* fusion-positive TC analysis set

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (95% CI)
Overall	[redacted]	[redacted]	[redacted]	[redacted]

Age				
<65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
Any metastatic disease				
Yes	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: complete response; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; IRC: independent review committee; NE: not estimable; NR: not reached; ORR: objective response rate; PR: partial response; RET: rearranged during transfection; TC: thyroid cancer.
Sources: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Subgroup analysis by *RET* mutation

ORR and DOR by type of *RET* mutation for the systemic therapy naïve TC analysis set are presented in Table 37. DOR by mutation type was [redacted] for the majority of fusion types, with the exception of CCDC6 fusion [redacted].

The ORR and DOR by type of molecular test are also presented in Table 37. Patients were most commonly tested with [redacted]

Table 37: ORR and DOR by *RET* mutation type and type of molecular assay based on IRC assessment for the systemic therapy naïve *RET* fusion-positive TC analysis set

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
***RET* mutation type**				
CCDC6	[redacted]	[redacted]	[redacted]	[redacted]
NCOA4	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
KIAA1217	[redacted]	[redacted]	[redacted]	[redacted]
TRIM24	[redacted]	[redacted]	[redacted]	[redacted]
Type of *RET* molecular assay				
NGS on Blood or Plasma	[redacted]	[redacted]	[redacted]	[redacted]
NGS on Tumour	[redacted]	[redacted]	[redacted]	[redacted]

FISH	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: complete response; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence in situ hybridisation; IRC: independent review committee; NA: not applicable; NE: not estimable; NR: not reached; ORR: objective response rate; PR: partial response; RET: rearranged during transfection; SD: stable disease; TC: thyroid cancer.
Sources: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Subgroup analysis by number and type of prior therapy

ORR and DOR by number or type of prior therapy are presented in Table 38. ORR was broadly consistent across the number of prior therapies. DOR was [redacted] for the number of prior therapy subtypes, with the exception of the one prior therapy subgroup (DOR: [redacted]).

Table 38: ORR and DOR by number and type of prior therapy based on IRC assessment for the systemic therapy naïve *RET* fusion-positive TC analysis set

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior therapies[a]				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]

[a] Multiple rounds of radioactive iodine therapy were considered as separate therapies.
Abbreviations: DOR: duration of response; IRC: Independent Review Committee; NA: not applicable; NE: not estimable; NR: not reached; ORR: objective response rate.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Forest plot summary for ORR analyses

All ORR subgroup analyses performed for the systemic therapy naïve *RET* fusion-positive TC analysis set are also summarised in Figure 26.

Figure 26: Forest plot of ORR in subgroup populations based on IRC assessment for systemic therapy naïve patients with RET fusion-positive TC

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IRC: independent review committee; NGS: next generation sequencing; ORR: overall response rate; PCR: polymerase chain reaction; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

B.2.8 *Meta-analysis*

As LIBRETTO-001 is a single arm trial, it is not possible to conduct any form of meta-analysis, network meta-analysis (NMA) or anchored ITC to estimate relative efficacy for selpercatinib versus relevant comparators. As such, matching-adjusted unanchored ITCs and naïve ITCs versus studies investigating the efficacy of relevant comparators were conducted, as reported in Section B.2.9.

B.2.9 *Indirect and mixed treatment comparisons*

- LIBRETTO-001 is a single-arm trial, meaning ITCs were required to inform the relative efficacy estimates for selpercatinib versus the relevant comparators for this submission: cabozantinib and BSC, based on the EXAM trial (*RET*-mutant MTC), and lenvatinib and BSC based on the SELECT trial (*RET* fusion-positive TC).
    - ITCs of selpercatinib versus sorafenib based on the DECISION trial (*RET* fusion-positive TC) are also presented for completeness.

RET-mutant medullary thyroid cancer

- In the *RET*-mutant MTC population, ITCs, in the form of matching-adjusted indirect comparisons (MAICs), were conducted for PFS and OS in line with the methodology proposed in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[71, 84, 85]
- Clinical effectiveness results were not reported separately for systemic therapy-naïve and systemic therapy experienced patients in EXAM. Therefore, the any-line pooled MTC population (n=295) from the LIBRETTO-001 trial was used in the MAIC, to more closely match the characteristics of the *RET*-mutant subgroup of the EXAM trial and provide a larger data set.
    - No OS data were available from the EXAM trial for a *RET*-mutant subgroup. As such, the unweighted curves for the *RET* M918T-positive subgroup receiving cabozantinib (n=81) or placebo (n=45) in the EXAM trial were compared to the weighted curve for the any-line LIBRETTO-001 population.[54] 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.[86, 87]
- For the comparison of selpercatinib versus cabozantinib, after weighting, the results of the MAIC demonstrate a statistically significant treatment benefit in terms of both OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).
- For the comparison of selpercatinib versus BSC (using placebo as a proxy), the results of the MAIC demonstrate a statistically significant treatment benefit in terms of both OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).

RET fusion-positive thyroid cancer

- In the *RET* fusion-positive TC population, it was not feasible to conduct MAICs, due to small patient numbers and a lack of comparability between LIBRETTO-001 and the comparator trials (SELECT and DECISION). As such, naïve ITCs were conducted to generate comparative efficacy estimates for selpercatinib versus lenvatinib and BSC, as well as sorafenib for completeness.
- The SELECT trial for lenvatinib included both systemic therapy (TKI or MKI) naïve and experienced patients, and OS data were only reported for the ITT population (including both systemic therapy naïve and experienced patients). The DECISION trial for sorafenib included only those patients who had not received prior targeted cancer therapy (including TKIs or MKIs). OS and PFS results from DECISION were reported for the intention-to-treat (ITT) population.
    - In order to facilitate comparisons with both trials, the pooled, any-line TC population (n=65) from the LIBRETTO-001 trial was used in the ITCs to more closely match the comparator populations.
- 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, aligned with assumptions used in prior NICE appraisals TA535 and TA742.[2, 25]
- For the comparison of selpercatinib versus lenvatinib (based on SELECT), the results of the naïve ITC demonstrate a statistically significant treatment benefit in terms of both OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).
- For the comparison of selpercatinib versus BSC (using placebo from SELECT as a proxy), the results of the naïve ITC demonstrate a statistically significant treatment benefit in terms of both

OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).

- Comparisons of selpercatinib versus sorafenib (via the DECISION trial) should be interpreted with caution, based on clinical plausibility concerns with the sorafenib OS data when compared to lenvatinib. The results of the naïve ITC demonstrate a statistically significant treatment benefit in terms of PFS (PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). While a numerical treatment benefit in OS was demonstrated for selpercatinib versus sorafenib, this result was not statistically significant (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).

Conclusion

- Overall, the ITCs conducted to generate comparative efficacy evidence for selpercatinib versus relevant comparators used the best available data and methods outlined in NICE DSU TSD 18.[71]
- Selpercatinib demonstrates clinically meaningful and statistically significant treatment benefits versus the primary comparators in UK clinical practice: cabozantinib (*RET*-mutant MTC) and lenvatinib (*RET* fusion-positive TC).

As discussed in Section B.1.1, an SLR was conducted in September 2019, and a subsequent update conducted in May 2023, to identify all relevant clinical evidence on the efficacy and safety of selpercatinib and potential comparators for the treatment of patients with *RET*-altered solid tumours, including *RET* fusion-positive TC and *RET*-mutant MTC. LIBRETTO-001 is a single-arm trial, and no head-to-head trials with available data comparing selpercatinib to the relevant comparators were identified in the clinical SLR. Beyond the studies formally identified in the clinical SLR, the LIBRETTO-531 trial exists, in which selpercatinib is being investigated versus cabozantinib or vandetanib in patients with advanced *RET*-mutant MTC who had not previously received cabozantinib or vandetanib. Due to the immaturity of this trial data, LIBRETTO-531 was not deemed suitable to inform comparative efficacy estimates in this submission.

Therefore, ITCs were conducted to inform the comparative efficacy estimates for selpercatinib versus the relevant comparators for this appraisal. In the *RET*-mutant MTC population, the relevant comparators are cabozantinib and BSC, and in the *RET* fusion-positive TC population, the relevant comparators are lenvatinib, sorafenib and BSC. The following section provides an overview of the ITC methodology and results for the *RET*-mutant MTC population and the *RET* fusion-positive TC population, in Section B.2.9.1 and Section B.2.9.2 respectively.

B.2.9.1 *RET*-mutant medullary thyroid cancer

Methodology of the indirect treatment comparison

Data sources

For patients with advanced *RET*-mutant MTC who have not received prior systemic therapy, the relevant comparators are cabozantinib and BSC. Based on feedback from UK clinical experts obtained during interviews conducted to support this submission, 80 to 90% of patients currently received cabozantinib, positioning it as the primary comparator to selpercatinib in the *RET*-mutant MTC population.[3] As discussed in Section B.1.1, an SLR and subsequent update have been 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. Of relevance to this submission, only

one trial was identified investigating cabozantinib in patients with advanced MTC: the EXAM trial.[54, 87, 88]

The EXAM trial was an international, double-blind, randomised placebo-controlled Phase III study enrolling patients with locally advanced or metastatic MTC. In total, n=214 patients were randomised to cabozantinib (140 mg BID), while n=109 patients were randomised to placebo. While positive *RET*-mutation status was not required in the EXAM trial, baseline characteristics (for the cabozantinib arm) and PFS results were available for a *RET*-mutant subgroup of the patient population.[88] However, OS KM data were only reported for a *RET* M918T-positive subgroup.[54] Clinical effectiveness results were also not reported separately for the systemic therapy-naïve and pre-treated patient populations.

Populations included in the MAIC

The LIBRETTO-001 and EXAM trials included both systemic therapy-naïve and pre-treated patients. In the LIBRETTO-001 trial, patients enrolled in the MTC: Cab/Van analysis set (n=152) had received 1 or more lines of prior cabozantinib or vandetanib. Patients enrolled in the MTC: Cab/Van Naïve (n=143) were cabozantinib and vandetanib naïve. As outlined above, PFS and OS outcomes were not reported separately for the systemic therapy naïve and experienced patients in EXAM, as such, a pooled, any-line population from the LIBRETTO-001 trial (MTC: Cab/Van and MTC: Cab/Van Naïve; n=295) was selected for comparison in the ITC. This population was chosen to more closely match the characteristics of the EXAM trial population, providing 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. Furthermore, the any-line population provides a larger data set.

Baseline characteristics were available for a *RET*-mutant subgroup in the cabozantinib treatment arm of the EXAM trial. As such, the characteristics of the LIBRETTO-001 any-line MTC population and the EXAM *RET*-mutant population in the cabozantinib arm were compared. Availability of KM PFS curves for the *RET*-mutant subgroup in the EXAM trial enabled direct comparison with PFS results for the any-line MTC population (n=295) in the LIBRETTO-001 trial, however, as discussed above, OS KM data were not available for a *RET*-mutant population in EXAM. As such, the unweighted KM OS curves for a *RET* M918T-positive subgroup in both the cabozantinib and placebo arms were used as a proxy for the overall *RET*-mutant groups for comparison with the any-line MTC LIBRETTO-001 population.

Feasibility assessment

Further characteristics of the EXAM trial, in addition to the LIBRETTO-001 trial, along with a summary of the key trial outcomes are presented in Appendix D. The definition and ascertainment of study endpoints were similar among the trials.

The baseline characteristics of the trial populations used for matching are presented in Table 39. Key differences in the patient population characteristics include the following:

- The LIBRETTO-001 any-line trial population (mean age: [redacted] years) is slightly older than the EXAM trial population, in both the cabozantinib (mean age: 55.0 years)
- The percentage of male patients in the LIBRETTO-001 any-line population (61.0%) is slightly lower than in EXAM, in the cabozantinib arm (68.2%)

- A lower proportion of patients had an ECOG performance status of 0 in the LIBRETTO-001 any-line population (37.6%) than in the EXAM trial population, in the cabozantinib arm (61.7%)
- The proportion of patients in the LIBRETTO-001 any-line population with prior MKI/TKI therapy ([redacted]%) was substantially higher than in the EXAM trial, in the cabozantinib arm (21.5%)
- The proportion of patients in the LIBRETTO-001 trial who had never smoked ([redacted]%) was higher than in the EXAM trial, in the cabozantinib arm (51.4%)
- The populations appeared to be similar for other reported characteristics

Prognostic factors and treatment-effect modifiers in patients with MTC were identified in the SLR and were validated with clinical experts experienced in the treatment of thyroid cancer during interviews conducted to support this appraisal.[3] The findings identified by the SLR for prognostic factors and treatment effect modifiers 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 in the EXAM trial. Based on the reported prognostic factors, outcomes in the LIBRETTO-001 trial may be expected to be worse than those in the EXAM trial, due to older age, worse ECOG 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 prior clinical expert feedback obtained during the NICE appraisal TA742.[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 ITC to estimate relative efficacy versus relevant comparators. As such, an unanchored MAIC versus the EXAM trial was explored to generate relative efficacy estimates versus cabozantinib and placebo. The placebo arm of the EXAM trial is considered a suitable proxy for BSC, as determined in TA516.[24]

Methodology

Populations included in the MAIC

Based on the data available from the EXAM trial, an unanchored population-adjusted ITC was conducted using individual patient-level data (IPD) from the any-line pooled population from the LIBRETTO-001 trial (MTC: Cab/Van and MTC: Cab/Van Naïve; n=295) and summary data from the EXAM trial, as reported in Schlumberger et al. (2017) and Sherman et al. (2016).[54, 87]

Due to similarities of baseline characteristics of the EXAM cabozantinib trial population and the any-line MTC population from LIBRETTO-001, as supported by clinical experts experienced in the treatment of TC and MTC interviewed for this appraisal, all patients in the any-line MTC population from LIBRETTO-001 were then included in the matched set.[3]

Endpoints of interest and statistical methods

MAICs were conducted for PFS and OS whereby outcomes in the LIBRETTO-001 trial were estimated using the method of moments approach, in line with the methodology proposed in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[71, 84, 85]

The MAIC adjusted for clinically important baseline characteristics that were known prognostic variables or treatment effect modifiers and were reported in both the LIBRETTO-001 trial and EXAM trial publication. As highlighted previously, prognostic factors and treatment effect modifiers in patients with MTC were identified in an SLR (Appendix D) and validated with clinical experts experienced in the treatment of thyroid cancer interviewed to support this appraisal.[3] The variables included in the adjustment were:

- Age
- Weight
- ECOG performance score
- Sex
- Smoking status
- *RET* M918T mutation status
- Prior MKI treatment

To balance the baseline characteristics between LIBRETTO-001 and EXAM, the selected LIBRETTO-001 patients were assigned weights such that the weighted mean baseline characteristics in LIBRETTO-001 patients exactly matched those reported for patients in EXAM (specifically, the *RET*-mutant subgroup treated with cabozantinib).

Weights meeting these conditions were obtained from a logistic regression model for the propensity of inclusion in the LIBRETTO-001 trial versus the EXAM trial, 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 trial, 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 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.

- The unweighted PFS curves for the *RET*-mutant population receiving cabozantinib (n=107) or placebo (n=62) in the EXAM trial digitised from Sherman *et al.* (2016) were compared to the weighted curve for the any-line LIBRETTO-001 population[87]

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.

- As discussed, no OS KM data were available from the EXAM trial for the *RET*-mutant subgroup. As such, the unweighted curves for *RET* M918T-positive patients receiving cabozantinib (n=81) or placebo (n=45) in the EXAM trial digitised from Schlumberger *et al.* (2017) were compared to the weighted curve for the any-line LIBRETTO-001 population as a proxy for the *RET*-mutant subgroup[54]
    - 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])[54, 87] As such, the treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated

Results of the MAIC

Baseline characteristics

A summary of the baseline characteristics of the selpercatinib (prior to and after matching), cabozantinib and BSC populations included in the MAIC are provided in Table 39.

Given the similarity between the 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 were exactly balanced between the two study populations. After weighting, the effective sample size (N_{eff}) for the MTC any-line population in LIBRETTO-001 was [redacted].

The distribution of weights is presented in Figure 27, 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.[71] Rescaling had very limited impact on the results.

Table 39: Matching baseline characteristics between LIBRETTO-001 and EXAM before and after matching

	LIBRETTO-001 any-line (before matching; N=295)	LIBRETTO-001 any-line (after matching; N_{eff}=[redacted])	EXAM *RET*-mutant cabozantinib (N=107)
Age, mean (SD)	[redacted]	[redacted]	55.0 (15.2)
Weight (kg), mean (SD)	[redacted]	[redacted]	74.0 (21.0)
ECOG PS 0 (%)	37.6	[redacted]	61.7
Sex (% male)	61.0	[redacted]	68.2
Smoking (% never)	[redacted]	[redacted]	51.4
RET M918T mutation positive (%)	[redacted]	[redacted]	74.6
Prior TKI/MKI therapy (%)	[redacted]	[redacted]	21.5

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; MKI: multi-kinase inhibitor; N_{eff}: effective sample size; *RET*: rearranged during transfection; SD: standard deviation; TKI: tyrosine kinase inhibitor.
Source: Raez et al (2023).[75]

Figure 27: Distribution of weights in the MAIC

Abbreviations: MAIC: matching-adjusted indirect comparison.

Efficacy outcomes

The weighted comparisons of efficacy outcomes between selpercatinib in the LIBRETTO-001 trial and cabozantinib and placebo in EXAM are presented in Table 40 (using a Cox regression model). KM plots for PFS and OS before and after weighting are presented in Figure 28 and Figure 29, respectively. The results of proportional hazards assessments are presented in Appendix O.

After weighting, the differences between treatment benefit in PFS remained significant and clinically meaningful for selpercatinib versus cabozantinib (HR: [redacted]; 95% CI: [redacted], [redacted] p[redacted]) and placebo (HR: [redacted]; 95% CI: [redacted], [redacted] p[redacted]). The differences between treatments in OS after weighting were also significant for selpercatinib versus cabozantinib (HR: [redacted]; 95% CI: [redacted], [redacted] p[redacted]) and placebo (HR: [redacted]; 95% CI: [redacted], [redacted] p[redacted]).

As highlighted above, 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-positive disease, and cabozantinib is known to be more effective in the M918T population compared with the overall *RET*-mutant population.

Table 40: Comparison of PFS and OS for selpercatinib (LIBRETTO-001) versus cabozantinib and placebo (EXAM) before and after matching

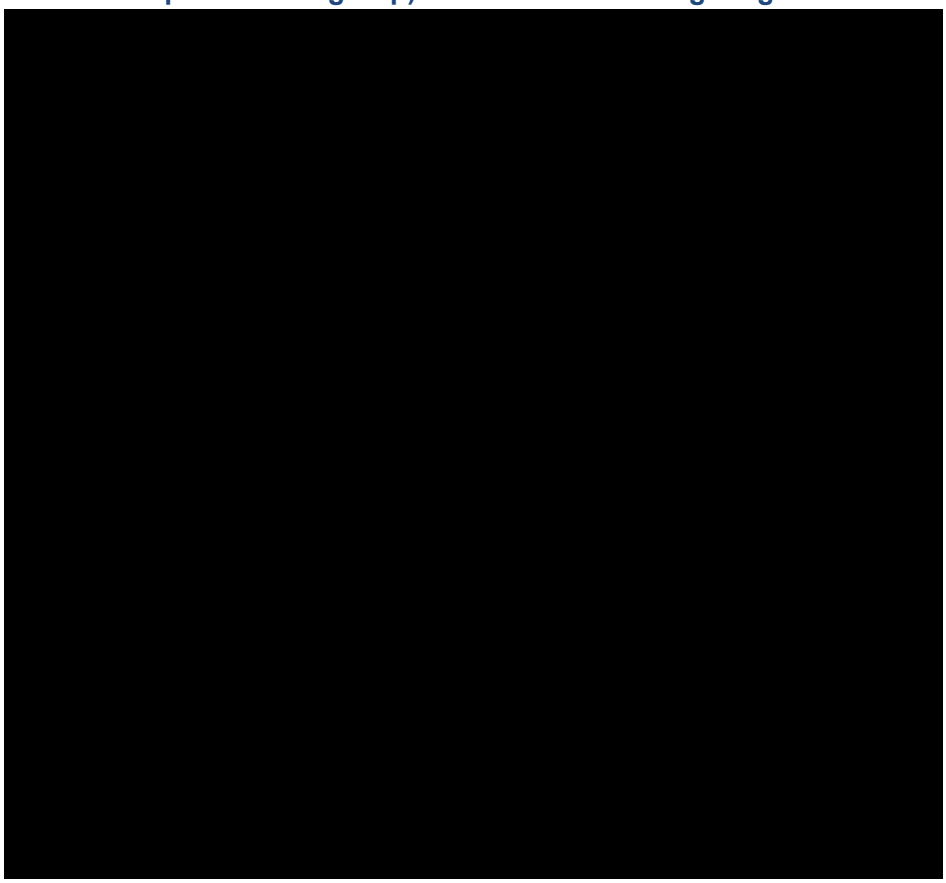
	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Selpercatinib versus cabozantinib				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib versus BSC (placebo)				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	[redacted]	[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 28: PFS (IRC assessment) for selpercatinib (LIBRETTO-001) versus cabozantinib and placebo (EXAM *RET*-mutant subgroup) before and after weighting

Abbreviations: IRC: independent review committee; PFS: progression free survival; PH: proportional hazards; RET: rearranged during transfection.

Figure 29: OS 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 (OS KM 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 (Appendix O).
Abbreviations: KM: Kaplan-Meier; OS: overall survival; PFS: progression free survival; PH: proportional hazards.

B.2.9.2 *RET* fusion-positive thyroid cancer

Methodology of the indirect treatment comparison

Data sources

For patients with advanced *RET* fusion-positive TC, lenvatinib and BSC represent the relevant comparators for selpercatinib, with lenvatinib representing the primary comparator that the majority of patients currently receive.[3] Clinical expert opinion suggests that lenvatinib is the dominant choice in clinical practice over sorafenib,[24] with 80 to 85% of patients with advanced *RET* fusion-positive TC receiving lenvatinib and 5 to 10% receiving sorafenib, as confirmed by UK clinical experts during interviews conducted to support this appraisal.[3] For completeness, results of the ITC of selpercatinib versus sorafenib are presented in this submission.

Following the initial feasibility assessment, the SELECT (lenvatinib versus placebo) and DECISION (sorafenib versus placebo) trials were further considered for inclusion in the ITCs and are discussed in the following feasibility assessment.

Feasibility assessment

Trial and patient characteristics

Both SELECT and DECISION were Phase III, double-blind, parallel-group RCTs. SELECT included 261 adult patients with DTC (including a PTC sub-population) with evidence of radioactive iodine-refractory disease and DECISION included 207 patients with locally advanced or metastatic radioactive iodine-refractory DTC progressing within the previous 14 months according to RECIST.[89, 90] Patients received lenvatinib 24 mg, orally QD, or sorafenib 400 mg, orally BID, in the SELECT and DECISION trials respectively, or a matching placebo. A top-line summary of the SELECT and the DECISION trial designs is presented in Table 18, Appendix D.

Baseline characteristics of patients in the LIBRETTO-001, DECISION and SELECT trials are presented in Table 41. Subgroup analyses for a *RET* fusion-positive population were not reported for OS or PFS in either DECISION or SELECT. As such, baseline characteristics are reported for the ITT populations.

In the SELECT and DECISION trials, patients were required to be refractory to radioactive iodine locally advanced or metastatic DTC for inclusion. The SELECT trial only allowed patients with one or no prior TKI or MKI therapy to be included, while the DECISION trial included patients who had received no prior targeted (including TKI or MKI) cancer therapy. For the SELECT and DECISION trials, the characteristics of the ITT population are presented for patients with advanced DTC receiving lenvatinib or placebo and sorafenib or placebo, respectively.

In the SELECT trial, ORR and PFS data were reported separately for the systemic therapy naïve and experienced subgroups. However, OS data were only available for the ITT population, including patients who were systemic therapy naïve and systemic therapy experienced. As the DECISION trial included only patients who had not received any prior targeted therapy, results reported for the ITT population represented a systemic therapy naïve population. Due to the lack of OS data available in the systemic treatment naïve subgroup in the SELECT trial, the any-line pooled TC population (n=65 patients) was selected for comparison in the ITC over the systemic therapy naïve (n=24) subgroup.

Key differences in the patient population characteristics in the trials include:

- [redacted]% of patients are advanced or metastatic *RET*-fusion positive in LIBRETTO-001, while no data are reported for a *RET*-fusion positive subgroup in either the SELECT or DECISION trial
- A higher proportion of patients were diagnosed with PTC in the LIBRETTO-001 trial ([redacted]%), compared with both the lenvatinib (50.6%) or placebo arm (51.9%) of the SELECT trial and the sorafenib (57.0) or placebo arm (56.7%) of the DECISION trial
- In LIBRETTO-001 (any-line), a higher proportion of patients had received at least 1 prior TKI or MKI ([redacted]%) compared with the lenvatinib (25.3%) and placebo arms (20.6%) of the SELECT trial and the sorafenib and placebo arm of the DECISION trial (in which no patients had received a prior MKI or TKI)
- In the any-line population of the LIBRETTO-001 trial, a lower proportion of patients had ECOG performance status 0 (38.5%) compared with the lenvatinib arm (55.2%) or placebo arm (51.9%) of the SELECT trial and the sorafenib arm (62.8%) or the placebo arm (56.7%) of the DECISION trial

During validation interviews conducted with clinical experts to support this submission, the experts stated that the presented baseline characteristics of the any-line LIBRETTO-001 TC population and the SELECT and DECISION trials were broadly similar and no clinically important differences were identified, with the exception of prior therapies received by patients.[3]

However, one clinical expert highlighted that the ECOG performance status of patients in the LIBRETT0-001 trial was generally poorer compared with the SELECT and DECISION trials. This would be expected to bias the ITC results against selpercatinib, when comparing with the SELECT and DECISION trials. The clinical experts also noted that the increased proportion of patients with PTC in the LIBRETTO-001 trial versus the comparator trials is to be expected due to the *RET* fusion-positive status of patients in the LIBRETTO-001 trial, which is uncommon in other subtypes of TC.[3, 36]

Table 41: Baseline characteristics of patients with TC enrolled in LIBRETTO-001, SELECT, and DECISION trials

Characteristic	LIBRETTO-001 (*RET*-fusion positive TC)	SELECT (ITT)[30]		DECISION (ITT)[41]	
	Selpercatinib (any-line) N=65	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Median age, years (range)	59 (20, 88)	64 (27, 89)	61 (21, 81)	63 (24, 82)	63 (30, 87)
Number (%) male	32 (49.2)	125 (47.9)	75 (57.3)	104 (50.2)	95 (45.2)
Ethnicity					
White	[redacted]	208 (79.7)	103 (78.6)	123 (59.4)	128 (61.0)
Black of African American	[redacted]	4 (1.5)	4 (3.1)	6 (2.9)	5 (2.4)
Asian	[redacted]	46 (17.6)	24 (18.1)	47 (22.7)	52 (24.8)
Other	[redacted]	3 (1.2)	0	2 (1.0)	2 (1.0)
Missing or uncodeable	[redacted]	NR	NR	29 (14.0)	23 (11.0)
Region, n (%)					
Europe	[redacted]	131 (50.2)	64 (48.9)	124 (59.9)	125 (59.5)
North America	[redacted]	77 (29.5)	39 (29.8)	36 (17.4)	36 (17.1)
Other	[redacted]	53 (20.3)	28 (21.4)	47 (22.7)	49 (23.3)
Median time from initial diagnosis, months (range)	[redacted]	66 (0.4, 573.6)	73.9 (6.0, 484.8)	66.2 (3.9, 362.4)	66.9 (6.6, 401.8)
ECOG performance status, n (%)					
0	25 (38.5)	144 (55.2)	68 (51.9)	130 (62.8)	129 (61.4)
1	36 (55.4)	104 (39.8)	61 (46.6)	69 (33.3)	74 (35.2)
2	4 (6.2)	12 (4.6)	2 (1.5)	7 (3.4)	6 (2.9)

3	[redacted]	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Not available	[redacted]	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Histology, n (%)					
Papillary	[redacted]	132 (50.6)	68 (51.9)	118 (57.0)	119 (56.7)
Poorly differentiated	[redacted]	28 (10.7)	19 (14.5)	24 (11.6)	16 (7.6)
Follicular, not Hürthle cell	[redacted]	53 (20.3)	22 (16.8)	13 (6.3)	19 (9.0)
Hürthle cell	[redacted]	48 (18.4)	22 (16.8)	37 (17.9)	37 (17.6)
Other	[redacted]	0 (0.0)	0 (0.0)	2 (1.0)	5 (2.4)
Missing or non-diagnosed	[redacted]	0 (0.0)	0 (0.0)	13 (6.3)	14 (6.7)
Metastases, n (%)					
Locoregional	[redacted]	4 (1.5)	0 (0.0)	7(3.4)	8 (3.8)
Distant	[redacted]	257 (98.5)	131 (100)	200 (96.6)	202 (96.2)
Prior MKI/TKI therapy					
Any prior therapy	[redacted]	66 (25.3)	27 (20.6)	0 (0.0)	0 (0.0)
Cabozantinib	[redacted]	NR	NR	NR	NR
Vandetanib	[redacted]	NR	NR	NR	NR
Sorafenib	[redacted]	NR	NR	NR	NR
Lenvatinib	[redacted]	NR	NR	NR	NR
Other MKI	[redacted]	NR	NR	NR	NR

*Anaplastic thyroid cancer
Abbreviations: ECOG: Eastern Cooperative Oncology Group; ITT: intention to treat; MKI: multi-kinase inhibitors; NR: not reported; TC: thyroid cancer; TKI: tyrosine kinase inhibitor.
Source: Raez et al (2023).[75]

Crossover between treatment arms

The patients in the placebo arm were allowed to crossover to lenvatinib or sorafenib after progression and continue in an open-label trial in the SELECT and DECISION trials, respectively. Among 114 eligible patients who received placebo and had tumour progression confirmed by independent review, 109 (95.6%) elected to receive open-label lenvatinib in the SELECT trial. In the DECISION trial, around 87.8% of patients receiving placebo crossed over to sorafenib treatment.[54, 90] For the SELECT trial, KM OS curves were adjusted to account for this treatment crossover (using rank-preserving structural failure time (RPSFT). Only unadjusted KM OS curves were available from the DECISION trial.

Summary of feasibility assessment

As discussed above, data from the LIBRETTO-001 trial are available for patients with *RET* fusion-positive advanced TC that are systemic therapy naïve (n=24). However, as OS KM data for a treatment-naïve population were not available in the SELECT trial for lenvatinib, comparisons were made with the pooled any-line TC population in LIBRETTO-001 (n=65). Furthermore, neither of the identified comparator trials reported outcomes in the RET-fusion positive TC subpopulation that would be comparable to the LIBRETTO-001 population. The placebo arms of DECISION and SELECT have previously been assessed as incomparable, and

so comparisons of selpercatinib with lenvatinib, placebo or sorafenib using either of these trials should be interpreted with caution.[91]

The placebo arms of the SELECT and DECISION trials represent the best available data for the efficacy of BSC in the *RET*-fusion positive TC population. As such, the placebo arms in both trials were explored as proxies for BSC in this submission. However, as discussed above, patients in either comparator trial were allowed to cross over to lenvatinib or sorafenib, likely affecting OS of the placebo arms in either trial. While the SELECT trial reported KM OS curves adjusted using RPSFT, the DECISION trial reported no KM OS data that had been adjusted for this cross-over (i.e. no use of RPSFT). As such, the KM OS curve for placebo in the DECISION trial is subject to potential confounding.

The OS comparison for selpercatinib versus placebo in the DECISION trial was ultimately not conducted, due to the potential confounding introduced by crossover. The SELECT trial also provides a slightly overall larger patient population (N=261) than the DECISION trial (N=207). As such, the SELECT trial was selected to represent the most appropriate proxy for BSC, which is aligned with the approach used in TA535 and TA742.[2, 25]

Given the LIBRETTO-001 trial does not include a control arm, it was not possible to conduct a NMA or anchored ITC to estimate relative efficacy versus relevant comparators. In addition, due to the lack of comparability between the trial populations and small patient numbers in LIBRETTO-001, an adjusted MAIC was considered infeasible. As such, naïve comparisons of selpercatinib versus lenvatinib and placebo (from SELECT), and versus sorafenib (from DECISION) were conducted.

Methodology

Populations included in the ITC

Based on data availability, a naïve comparison was conducted using IPD from the any-line population from the LIBRETTO-001 trial (n=65) versus the SELECT and DECISION trials.

Neither of the identified comparator trials reported outcomes in the *RET*-fusion positive TC subpopulation that would be comparable to the LIBRETTO-001 population. As discussed in Section B.1.3.1 there is a lack of consensus in the published literature as to whether *RET*-alterations in TC are associated with a different prognosis versus wild-type TC, thus, uncertainty as to whether *RET* alteration status may be considered as a prognostic factor.[26, 42] As highlighted above, clinical experts considered that there were no clinically important differences in the presented baseline characteristics in each of the populations in the LIBRETTO-001, the SELECT and the DECISION trials.[3]

Statistical methodology

The patient-level KM data was reconstructed by digitising published KM curves from comparator trials. The Cox PH regression was fitted to reconstructed KMs data and selpercatinib data to estimate HRs and 95% CIs for selpercatinib versus the comparators (lenvatinib, sorafenib, and placebo). Non-parametric log-rank tests were used to evaluate statistical significance.

Results of the ITC

PFS

As outlined above, in the absence of data for patients with advanced or metastatic *RET*-fusion positive TC, the published OS and PFS data from the ITT populations of the SELECT and DECISION trials are considered in this section.

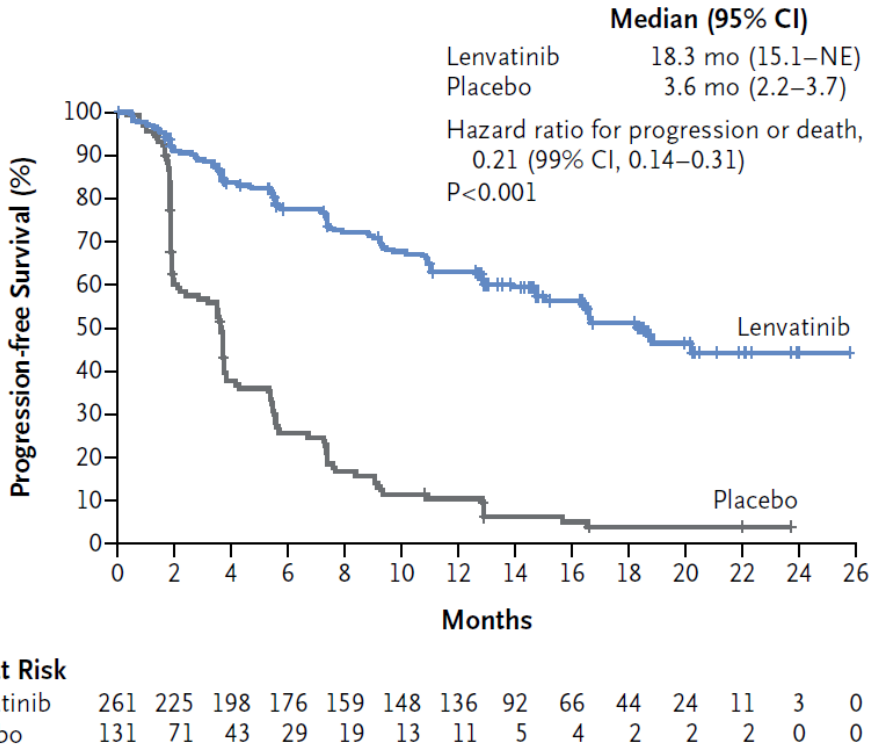
An overview of the PFS data for LIBRETTO-001, SELECT and DECISION is presented in Table 42. KM curves of PFS for lenvatinib and placebo (from SELECT) and sorafenib and placebo (from DECISION) are presented in Figure 30 and Figure 31, respectively. The KM curve of PFS for the any-line TC population from selpercatinib is presented in Figure 20, Section B.2.6.2.

Table 42: PFS for the LIBRETTO-001, SELECT, and DECISION trials

	LIBRETTO-001 (*RET*-fusion positive TC)	SELECT		DECISION	
	Selpercatinib (any-line) (N=65)	Lenvatinib (N=261)	Placebo (N=131)	Sorafenib (N=207)	Placebo (N=210)
Median PFS (95% CI), months	[redacted]	18.3 (15.1, NE)	3.6 (2.2, 3.7)	10.8	5.8
HR (95% CI)	NA	0.21 (0.14, 0.31)		0·59 (0.45, 0.76)	
p-value	NA	<0.001		<0.001	
PFS rate (%)					
6 months (95% CI)	[redacted]	77.5 (71.7, 82.3)	25.4 (18.0, 33.6)	NR	NR
12 months (95% CI)	[redacted]	63.0 (56.5, 68.9)	10.5 (5.7, 16.9)	NR	NR
18 months (95% CI)	[redacted]	51.1 (43.3, 58.3)	3.8 (1.1, 9.2)	NR	NR
24 months (95% CI)	[redacted]	44.3 (35.1, 53.1)	NE	NR	NR
Median follow-up duration (months)	[redacted]	17.1[a]	17.4[a]	16.2[b]	

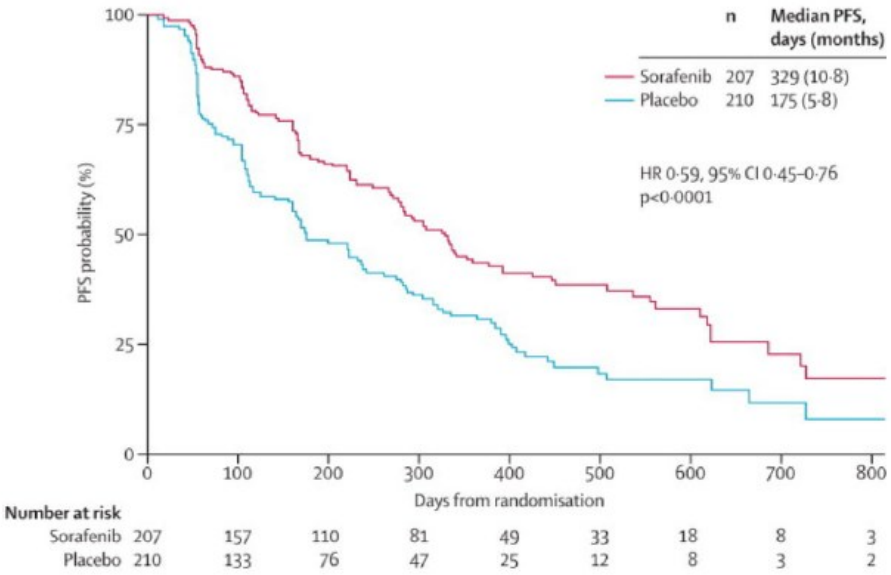
[a] Schlumberger et al. (2015) reports median follow-up for lenvatinib and placebo but it does not specify for which outcome. [b] Brose et al. (2014) reports median follow-up irrespective of the treatment arm.
Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not applicable; NE: not estimated; NR: not reported; PFS: progression-free survival
Sources: Raez *et al* (2023),[75], Schlumberger *et al* (2015),[89] Brose *et al.* (2014).[90]

Figure 30: KM of PFS for patients receiving lenvatinib versus placebo in the SELECT trial (ITT population)



Abbreviations: CI: confidence interval; NE: not estimated; PFS: progression-free survival.
Source: Schlumberger *et al.* (2015)[89]

Figure 31: KM of PFS for patients receiving sorafenib versus placebo in the DECISION trial (ITT population)



Abbreviations: CI: confidence intervals; HR: hazard ratio; PFS: progression-free survival.
Source: Brose et al. (2014).[90]

The results of the naïve comparison of PFS for selpercatinib in the LIBRETTO-001 trial (any-line population) versus lenvatinib and placebo in SELECT, and sorafenib and placebo in the DECISION trial are presented in Table 43.

The comparison demonstrates a statistically significant improvement in PFS for selpercatinib versus lenvatinib (HR: [redacted] [95% CI: [redacted], [redacted]; p<[redacted]]) and versus placebo (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). In addition, there was a statistically significant improvement in PFS for selpercatinib versus sorafenib (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]) and versus placebo (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).

Table 43: Comparison of PFS for selpercatinib (LIBRETTO-001, any-line) versus lenvatinib and placebo (SELECT) and versus sorafenib and placebo (DECISION)

Treatment Comparison	PFS	
	HR (95% CI)	p-value
LIBRETTO-001 versus SELECT		
Selpercatinib versus lenvatinib	[redacted]	[redacted]
Selpercatinib versus placebo	[redacted]	[redacted]
LIBRETTO-001 versus DECISION		
Selpercatinib versus sorafenib	[redacted]	[redacted]
Selpercatinib versus placebo	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival.

For DECISION and SELECT trials, OS was only reported for the overall ITT population. A summary of OS results from the LIBRETTO-001, DECISION and SELECT trials are provided in Table 44.

Patients in the placebo arm were allowed to cross over to lenvatinib at disease progression in SELECT. The majority of patients in the placebo arm crossed over (109 [95.6%] of patents who had experienced tumour progression).[54] This likely affected the OS of the control arm and was addressed by adjusting outcomes using a RPSFT model for patients receiving placebo.[91] KM curves for OS from SELECT before and after adjustment are presented in Figure 32.[25]

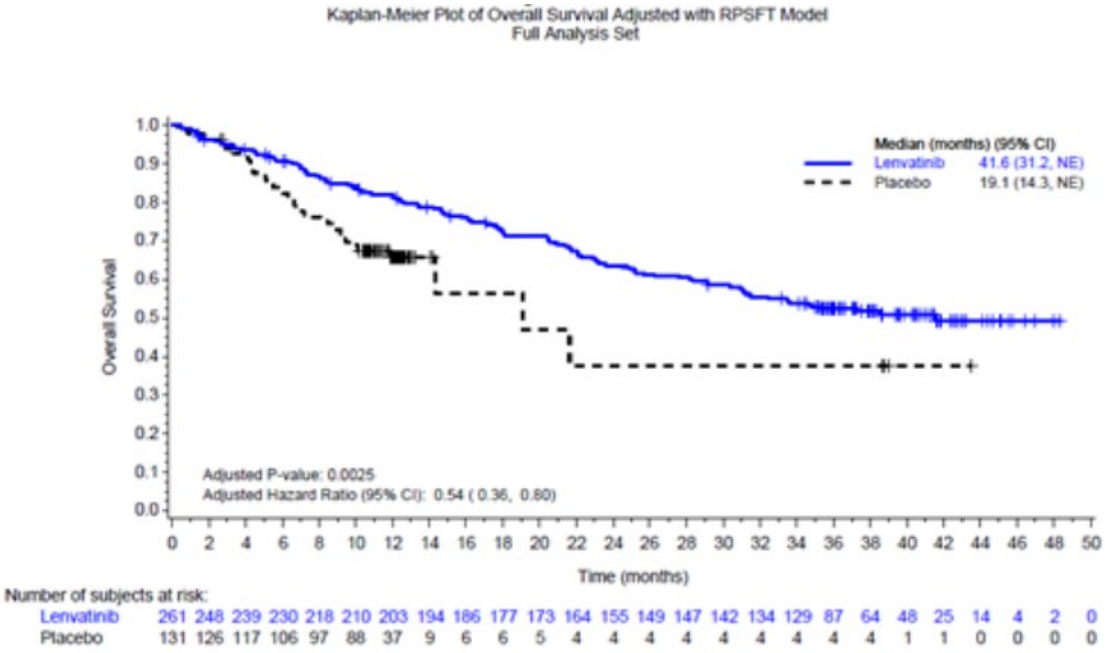
For the DECISION trial, OS was only reported for the ITT population. KM curves for OS for sorafenib versus placebo are presented in Figure 33. Patients receiving placebo in DECISION were permitted to cross over to sorafenib and no adjusted (e.g., by using RPSFT) results were reported; around 87.8% patients had switched over to sorafenib from placebo in DECISION trial. Thus, the OS curve for placebo is subject to potential confounding.[90]

Table 44: OS in the LIBRETTO-001, SELECT, and DECISION trials

	LIBRETTO-001 (*RET*-fusion positive TC)	SELECT		DECISION	
	Selpercatinib (any-line) N=65	Lenvatinib (ITT) N=261	Placebo (ITT) N=131	Sorafenib (ITT) N=207	Placebo (ITT) N=210
Median OS (95% CI), months	[redacted]	*41.6 (31.2, NE)	*34.5 (21.7, NE)	NR	NR
HR (95% CI)	[redacted]	*0.54 (0.36, 0.80; p=0.0025)			
OS rate (%)					
6 months (95% CI)	[redacted]	NR	NR	NR	NR
12 months (95% CI)	[redacted]	NR	NR	NR	NR
18 months (95% CI)	[redacted]	NR	NR	NR	NR
24 months (95% CI)	[redacted]	NR	NR	NR	NR
Median follow-up duration (months)	[redacted]	Data cut-off date: 21 August 2015[a]		16.2	

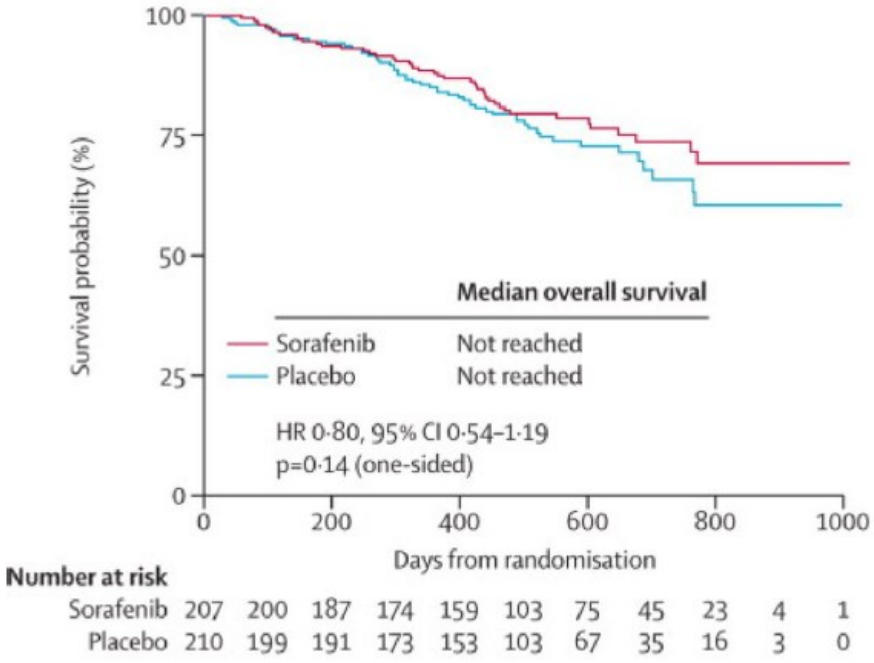
*RPSFT adjusted, ITT population. [a] The median follow-up for the 3rd data cut-off for SELECT that was used to inform OS for lenvatinib and placebo was not reported. [b] Brose et al. (2014)[90] reports median follow-up irrespective of the treatment arm.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR#: not reported; NR: not reached; NE: not estimable; OS: overall survival; PFS: progression free survival; RPSFT: Rank-preserving structural failure time.
Sources: Raez *et al* (2023),[75] Brose *et al.* (2014)[90], Schlumberger *et al*. (2015)[89]

Figure 32: RPSFT-adjusted and unadjusted KM curves of OS for patients receiving lenvatinib versus placebo in the SELECT trial



Abbreviations: CI: confidence interval; HR: hazard ratio; PI: placebo; RPSFT: rank preserving structural failure time model.
Source: NICE TA535.[91]

Figure 33: KM curve for OS among patients receiving sorafenib versus placebo in the DECISION trial



Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival.
Source: Brose *et al.* (2014)[90]

The results of the naïve comparison of OS for selpercatinib in the LIBRETTO-001 trial (any-line) versus lenvatinib and placebo in SELECT, and sorafenib in the DECISION trial are presented in Table 45.

The comparison demonstrates a statistically significant improvement in OS for selpercatinib versus lenvatinib (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]) and versus placebo (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). The improvement in OS also indicates a numerical treatment benefit for selpercatinib versus sorafenib, though statistical significance was not reached (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). Due to potential bias resulting from crossover of patients from placebo to sorafenib, the comparison of OS for selpercatinib versus placebo in the DECISION trial was not conducted.

Table 45: Comparison of OS for selpercatinib (LIBRETTO-001, any-line) versus lenvatinib and placebo (SELECT) and versus sorafenib and placebo (DECISION)

Treatment Comparison	OS	
	HR (95% CI)	p-value
LIBRETTO versus SELECT		
Selpercatinib versus lenvatinib	[redacted]	[redacted]
Selpercatinib versus placebo	[redacted]	[redacted]
LIBRETTO versus DECISION		
Selpercatinib versus sorafenib	[redacted]	[redacted]
Selpercatinib versus placebo	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not analysed (due to crossover-adjusted data not reported); OS: overall survival.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

Strengths and weaknesses of the analyses

RET-mutant MTC

In alignment with NICE DSU TSD 18,[71] the effect modifiers and prognostic variables to be included for adjustment in the MAIC were carefully considered; the variables to adjust for were identified via an evidence-based process which included an SLR and subsequent validation with experts in the field of TC and MTC. With these variables in mind, the analyses were conducted with the robust methodologies suggested in NICE DSU TSD 18 to produce high-quality comparative efficacy evidence for selpercatinib versus cabozantinib and BSC, in line with the approaches used and accepted as part of NICE TA742.[2, 71]

As with all ITCs, it is not possible to exclude all bias due to residual confounding and unobserved residual bias. In addition, 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. However, UK clinical experts interviewed to support the development of this submission confirmed that the variables adjusted for in the MAIC represent the most clinically important variables and, after adjustment, the selpercatinib and cabozantinib population showed very good matching.[3]

The MAICs were limited by comparator data availability. Firstly, clinical effectiveness results are not reported for treatment-naïve patients specifically in the *RET*-mutant subgroup of the EXAM trial. As such, it was not possible to conduct a MAIC using data specific to a treatment-naïve RET-mutant MTC population. Therefore, data from the any-line MTC population in LIBRETTO-001 were considered to represent the best dataset for selpercatinib to be compared versus the EXAM trial – the proportion of patients receiving prior MKI therapy was subsequently aligned between the two trials as part of the matching process to minimise any uncertainty relating to the prior treatment differences in the two trials.

No OS KM data were available from the EXAM trial for the *RET*-mutant subgroup, meaning that the unweighted curves for the *RET* M918T-positive receiving cabozantinib or placebo in the EXAM trial, digitised from the Schlumberger *et al.* (2017), were compared to the weighted curve for the any-line LIBRETTO-001 population.[54] Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutant population. As such, 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 were matched and weighted to the *RET*-mutant cabozantinib arm (although M918T status was included as a covariate in the Cox PH model). Therefore, the assumption was made that the baseline characteristics of these groups were equivalent.

The results of the MTC ITCs are supported by preliminary results from the LIBRETTO-531 trial, comparing selpercatinib versus cabozantinib or vandetanib in patients with advanced, systemic therapy naïve *RET*-mutant MTC, as detailed in Section B.2.6.3 and Appendix M. In LIBRETTO-531, selpercatinib was associated with a stratified PFS HR of 0.28 (95% CI: 0.16, 0.48) versus cabozantinib or vandetanib; in the subgroup analysis of PFS, selpercatinib was associated with a PFS HR of 0.22 (95% CI: 0.11, 0.41) versus cabozantinib specifically, supporting the results of the ITC that indicate selpercatinib substantially reduce the risk of disease progression or death compared to cabozantinib.

RET fusion-positive TC

As outlined above, naïve comparisons were conducted to derive comparative efficacy estimates for selpercatinib versus lenvatinib, sorafenib and placebo in the *RET* fusion-positive TC subgroup, due to the small patient numbers in all trials and lack of comparability between LIBRETTO-001, DECISION and SELECT. 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. However, during interviews conducted to support this submission, UK clinical experts confirmed that the baseline characteristics of the selpercatinib and comparator populations can be considered broadly comparable.[3]

As with the MAIC conducted for the *RET*-mutant MTC population, the comparative efficacy estimates for selpercatinib versus lenvatinib, sorafenib and BSC were limited by comparator data availability. Firstly, the SELECT and DECISION trials were not limited to a *RET* fusion-positive population; as outlined in Section B.1.3.1, the prognostic significance of *RET* fusion in TC is unclear, so there is potential for bias to be introduced. Thus, the efficacy data from SELECT and DECISION may not be generalisable to *RET* fusion-positive TC.

Furthermore, proportions of systemic therapy naïve and systemic therapy experienced patients differed between trials. In the SELECT trial, patients may have either received no systemic therapy (TKI or MKI) or one prior systemic therapy (TKI or MKI). In the DECISION trial, patients were not permitted to receive prior targeted therapy (including a TKI or MKI). Thus, prior systemic therapies received by patients in the LIBRETTO-001 trial differed from the SELECT and DECISION, and this discrepancy was not adjusted for in the naïve comparisons. As patients in DECISION were not permitted to receive any prior targeted therapy, when compared with the any-line TC LIBRETTO-001 population and the SELECT population, the efficacy data from DECISION are likely to be biased in favour of sorafenib.

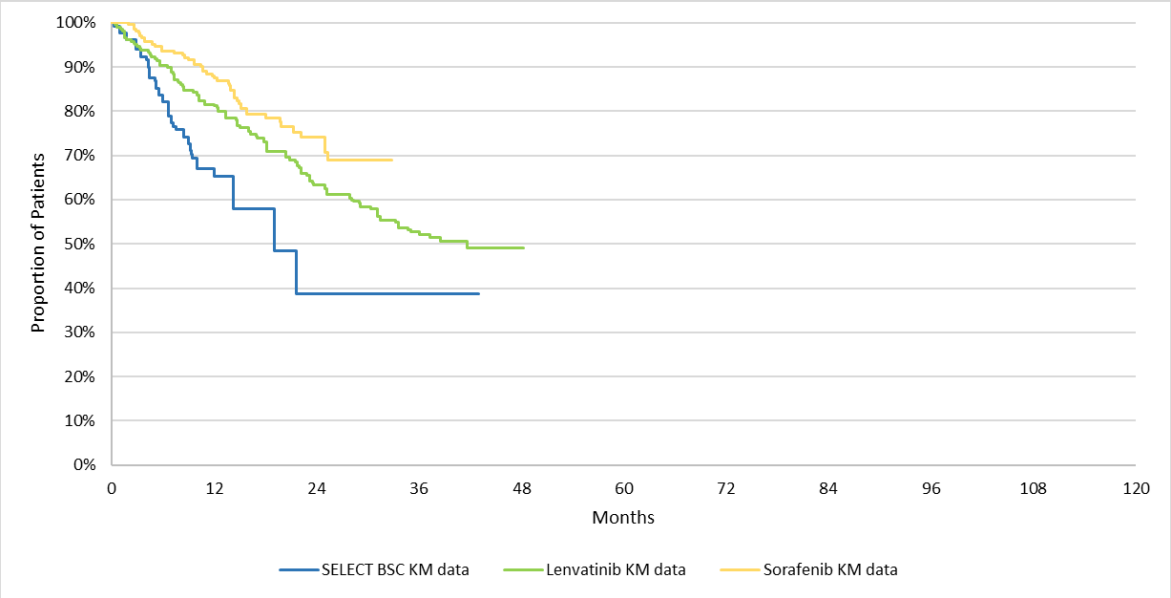
Moreover, given the higher proportion of patients receiving a prior systemic therapy in the LIBRETTO-001 trial, this difference may bias results against selpercatinib, as the LIBRETTO-001 patient population includes those patients who have already progressed on, or have discontinued, a systemic treatment. Therefore, these patients may represent a population with more advanced, or more severe disease; this is further supported by clinical expert opinion obtained as part of this submission, which indicated the lower proportion of patients in the LIBRETTO-001 trial with an ECOG performance score >0 may bias against selpercatinib when compared with the SELECT and DECISION trials.

In both DECISION and SELECT, crossover from the placebo to the lenvatinib or sorafenib arm, respectively, was permitted; as such, OS was confounded by crossover. KM curves for OS that had been adjusted for crossover using a RPSFT model were available for SELECT, but adjusted OS KM curves were not available for DECISION. The potential introduction of bias from the permitted crossover in the placebo arm of the DECISION trial resulted in the placebo arm in the SELECT trial ultimately being used to calculate the comparative efficacy of selpercatinib versus BSC.

Finally, it should also be noted the OS comparison between selpercatinib and sorafenib should be interpreted with caution. When the sorafenib OS KM data from DECISION are compared to the OS KM data for lenvatinib and BSC and in the SELECT trial (Figure 34), the sorafenib data are associated with clinical plausibility concerns, indicating that the SELECT and DECISION trials represent substantially different patient populations.

A comparison of the PFS results of SELECT and DECISION highlight that lenvatinib results in substantially higher PFS (18.3 months) when compared with sorafenib (10.8 months; Table 42). This contrasts with the OS KM data from DECISION and SELECT, which indicate that sorafenib extends OS when compared to lenvatinib. It is not plausible for sorafenib to be associated with increased OS compared with lenvatinib, but substantially reduced PFS.

Figure 34: OS KM data for lenvatinib (SELECT), BSC (SELECT) and sorafenib (DECISION)



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

Improved OS for sorafenib versus lenvatinib is also at odds with the 'versus placebo' comparisons in both trials, where lenvatinib improves OS versus placebo (HR: 0.54) in the SELECT trial by a greater magnitude than sorafenib versus placebo (HR: 0.80) in the DECISION trial. Improved OS for lenvatinib versus sorafenib is also supported by UK clinical expert opinion obtained as part of this appraisal, estimating that sorafenib is associated with a plausible ten-year survival of 2.5%, compared to 5-10% for lenvatinib.[3]

These results are likely indicative of fundamental differences between the SELECT and DECISION trial populations, and suggest the DECISION trial may include a patient population with less severe disease and facing an improved prognosis, compared to those in the SELECT trial. For example, 25.3% of patients receiving lenvatinib in SELECT received a previous treatment, while no patients received previous treatment in the DECISION trial. To this extent, as part of TA535, the AG concluded that the risk profiles of the placebo arms of the two trials are not comparable.[25]

Considering this, the sorafenib OS KM data, and resulting ITC results for OS between selpercatinib and sorafenib are associated with high levels of uncertainty and must be interpreted with caution.

Summary of the results of the ITCs

For the comparison of selpercatinib versus cabozantinib in the *RET*-mutant MTC population, the results of the MAIC demonstrate a statistically significant treatment benefit in terms of both OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p<[redacted]]). For the comparison of selpercatinib versus placebo in the *RET*-mutant MTC population, the results of the MAIC demonstrate a statistically significant treatment benefit in terms of both OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). These comparisons adjusted for all identified prognostic factors and treatment effect modifiers that were consistently reported in the EXAM and the LIBRETTO-001 trials. Overall, in the *RET*-mutant

MTC population, the MAICs demonstrate a clinically meaningful and significant treatment benefit of selpercatinib versus both cabozantinib and placebo, which is a reasonable proxy for BSC.

For the comparison of selpercatinib versus lenvatinib (based on SELECT) in the *RET* fusion-positive TC population, the results of the naïve ITC demonstrate a statistically significant treatment benefit in terms of both OS and PFS (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). Similarly, the naïve ITC demonstrates selpercatinib statistically significantly improves OS and PFS versus BSC based on SELECT (OS HR: [redacted] [95% CI: [redacted], [redacted]; p-value[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]]; p<[redacted]].

For the comparison of selpercatinib versus sorafenib (based on DECISION) in the *RET* fusion-positive TC population, the results of the naïve ITC demonstrate a statistically significant treatment benefit in terms of PFS (HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). While a treatment benefit of selpercatinib was demonstrated versus sorafenib for OS, this benefit was [redacted]statistically significant (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). However as detailed above, the OS ITC between selpercatinib and sorafenib must be interpreted with extreme caution, given the clinical plausibility concerns associated with the sorafenib OS KM data from DECISION. Regardless, sorafenib is not considered a relevant comparator for selpercatinib in this indication.

Furthermore, as supported by clinical experts consulted as part of a validation exercise, lenvatinib is predominantly used over sorafenib to treat patients with advanced TC, due to a perceived improved efficacy and similar adverse event profile.[3] Thus, selpercatinib demonstrates statistically significant benefits in PFS and OS for the MKI primarily used in UK clinical practice to treat patients with advanced *RET* fusion-positive TC.

Overall, the ITCs conducted to generate comparative efficacy evidence for selpercatinib versus relevant comparators used the best available data and methods outlined in NICE DSU TSD 18.[71] In both the *RET*-mutant MTC and *RET* fusion-positive TC populations, selpercatinib demonstrates clinically meaningful and statistically significant treatment benefits versus relevant comparators in UK clinical practice, with numerical improvements observed for the comparison of OS between selpercatinib and sorafenib.

B.2.10 *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) with results from the *RET*-mutant MTC SAS (N=324) and the *RET*-fusion positive TC SAS (N=66) presented in this submission. Results from the OSAS (N=837) are presented in Appendix F.[70]
- In the *RET*-mutant MTC SAS and the *RET* fusion-positive TC SAS, Grade 3 or 4 TEAEs were reported by [redacted] and [redacted] patients, respectively, irrespective of relatedness to selpercatinib. Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication.
- Selpercatinib was well tolerated in both patient populations, with dose reductions required in [redacted] patients in the *RET*-mutant MTC SAS and [redacted] patients in the *RET* fusion-positive TC SAS, with the most common reason being due to AEs ([redacted] and [redacted] respectively).
- In both the *RET*-mutant MTC SAS and the *RET* fusion-positive TC SAS, permanent discontinuation of therapy due to TEAEs related to selpercatinib were infrequent (5.2% and 1.5%, respectively), with no predominant pattern among the individual AEs reported.[70]
- In LIBRETTO-001, the safety profile of selpercatinib was characterised by recognisable and addressable toxicities. As a result, permanent discontinuation of selpercatinib due to TEAEs was infrequent in both the *RET*-mutant MTC SAS and the *RET* fusion-positive TC 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 both *RET*-mutant MTC and *RET* fusion-positive TC patients, selpercatinib has demonstrated a positive risk: benefit ratio in these populations.

The following sections present the *RET*-mutant MTC SAS and the *RET* fusion-positive TC SAS enrolled in LIBRETTO-001 (see Table 5 for analysis set definitions). The *RET*-mutant MTC SAS includes N=324 patients with *RET*-mutant MTC, and the *RET* fusion-positive TC SAS includes N=66 patients with RET fusion-positive TC, with all patients treated with at least one or more doses of selpercatinib. The following section presents a summary of the safety data for the *RET*-mutant MTC SAS and the *RET* fusion-positive TC SAS as these populations inform the AEs for selpercatinib in the cost-effectiveness model (Section B.3.3.7).[70]

The OSAS provides a comprehensive summary of safety over all N=837 patients treated with at least one or more doses of selpercatinib, covering *RET*-altered cancer types enrolled in LIBRETTO-001. A summary of the safety data for the OSAS are presented in Appendix F.

B.2.10.1 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 BID. Table 46 summarises the range of starting doses for patients in the LIBRETTO-001 trial. The majority ([redacted] of the *RET*-mutant MTC SAS and [redacted]) of patients received a starting dose of 160 mg BID, with a small proportion receiving either >160mg BID (200–240mg BID; [redacted] patients in the *RET*-mutant MTC SAS and [redacted] patient in the *RET* fusion-positive TC SAS) or <160mg BID (20mg QD – 120mg BID; [redacted] patients in the *RET*-mutant MTC SAS and [redacted] patients in the *RET*-fusion positive TC SAS).

Table 47 presents the relative dose intensities received for the *RET*-mutant MTC SAS and *RET* fusion-positive TC SAS, with mean dose intensity of [redacted] and [redacted], respectively. Mean time on treatment (ToT) was [redacted] and [redacted] months, for patients in the *RET*-mutant MTC SAS and *RET* fusion-positive TC SAS, respectively.

A summary of dose modifications during the LIBRETTO-001 trial is also presented in Table 48. Dose reductions were observed in [redacted] patients in the *RET*-mutant MTC SAS and [redacted] patients in the *RET* fusion-positive TC SAS. The most common reason for dose reductions in both analysis sets was adverse events (occurring in [redacted] and [redacted] patients in the *RET*-mutant MTC SAS and *RET* fusion-positive TC SAS, respectively). Withheld doses were more common in both safety analysis sets, occurring for [redacted] patients in the *RET*-mutant MTC SAS and [redacted] patients in the *RET* fusion-positive TC SAS, respectively. Adverse events were also the most common reason for dose interruptions in both analysis sets (for [redacted] and [redacted] patients in the *RET*-mutant MTC SAS and *RET* fusion-positive TC SAS, respectively).

Table 46: Starting doses of selpercatinib

	***RET*-mutant MTC SAS (N=324)**	***RET* fusion-positive TC SAS (N=66)**
Starting dose, n (%)		
20 mg QD	[redacted]	[redacted]
20 mg BID	[redacted]	[redacted]
40 mg BID	[redacted]	[redacted]
60 mg BID	[redacted]	[redacted]
80 mg BID	[redacted]	[redacted]
120 mg BID	[redacted]	[redacted]
160 mg QD	[redacted]	[redacted]
160 mg BID	[redacted]	[redacted]
200 mg BID	[redacted]	[redacted]
240 mg BID	[redacted]	[redacted]

Abbreviations: BID: twice daily; MTC: medullary thyroid cancer; N: number of patients in safety analysis set; n: number of patients; QD: once daily; RET: rearranged during transfection; SAS: safety analysis set; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

Table 47: Selpercatinib time on treatment and relative dose intensity

	***RET*-mutant MTC SAS N=324**	***RET* fusion-positive TC SAS N=66**
Time on treatment, months		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[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; n: number of patients rearranged during transfection; SAS: safety analysis set; SD: standard deviation; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

Table 48: Selpercatinib dose modifications

	RET-mutant MTC SAS N=324	*RET* fusion-positive TC SAS N=66
Dose reduction, n (%)		
Any	[redacted]	[redacted]
AE	[redacted]	[redacted]
Intra-patient dose escalation	[redacted]	[redacted]
For other reason	[redacted]	[redacted]
Dose withheld, 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; n: number of patients; RET rearranged during transfection; SAS: safety analysis set; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

B.2.10.2 Summary of adverse events

A summary of TEAEs observed in LIBRETTO-001 is presented in Table 49. While TEAEs related to selpercatinib were experienced in the majority of patients, treatment-emergent serious adverse events (TE-SAEs) related to selpercatinib were comparatively uncommon, occurring in [redacted] and [redacted] patients in the *RET*-mutant MTC SAS and *RET* fusion-positive TC SAS, respectively. Furthermore, TEAEs leading to treatment discontinuation attributed to selpercatinib treatment were uncommon in 17 (5.2%) patients in the *RET*-mutant MTC SAS and 1 (1.5%) patient in the *RET* fusion-positive TC SAS.[70] [redacted] in the *RET*-mutant MTC SAS was attributed to selpercatinib treatment.

Overall, 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.

Table 49: Summary of TEAEs in the LIBRETTO-001 trial

	RET-mutant MTC SAS N=324	*RET* fusion-positive TC SAS N=66
Any TEAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Grade ≥3 TEAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
TEAE leading to permanent treatment discontinuation, n (%)		
All	30 (9.3)	2 (3.0)
Related to selpercatinib	17 (5.2)	1 (1.5)
TE-SAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Fatal TEAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; RET: rearranged during transfection; SAE: serious adverse event; SAS: safety analysis; TC: thyroid cancer; TE: treatment emergent; TEAE: treatment-emergent adverse event.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

Common treatment-emergent adverse events

Most patients in both analysis sets experienced at least one TEAE during treatment, with the most common TEAEs (reported for ≥15% of patients) summarised in Table 50. The most common any grade TEAEs in the *RET*-mutant MTC SAS were oedema [redacted], fatigue [redacted], diarrhoea [redacted], hypertension [redacted] and dry mouth (43.2%). The most common any grade TEAEs in the *RET* fusion-positive TC SAS were diarrhoea (54.5%), fatigue [redacted], dry mouth (50.0%), hypertension [redacted] and abdominal pain [redacted]. Overall, the rates of adverse events between the analysis sets were similar.[70]

Table 50: Common TEAEs by grade (15% or greater of patients per analysis set)

Preferred term	*RET*-mutant MTC SAS N=324		*RET* fusion-positive TC SAS N=66	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Oedema	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	22 (6.8)	36 (54.5)	5 (7.6)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	140 (43.2)	0 (0.0)	33 (50.0)	0 (0.0)
Hypertension	[redacted]	[redacted]	[redacted]	10 (15.2)
AST increase	118 (36.4)	25 (7.7)	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	0 (0.0)
Abdominal pain	[redacted]	[redacted]	[redacted]	3 (4.5)

ALT increase	107 (33.0)	29 (9.0)	[redacted]	[redacted]
Constipation	139 (42.9)	1 (0.3)	27 (40.9)	0 (0.0)
Nausea	127 (39.2)	5 (1.5)	20 (30.3)	0 (0.0)
Blood creatine increase	[redacted]	[redacted]	[redacted]	[redacted]
Headache	109 (33.6)	9 (2.8)	[redacted]	[redacted]
Cough	[redacted]	0 (0.0)	[redacted]	[redacted]
Vomiting	94 (29.0)	8 (2.5)	24 (36.4)	2 (3.0)
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	19 (28.8)	1 (1.5)
Back pain	[redacted]	[redacted]	17 (25.8)	2 (3.0)
Decreased appetite	[redacted]	[redacted]	19 (28.8)	1 (1.5)
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolongation	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	92 (28.4)	17 (5.2)	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECG: electrocardiogram; MTC: medullary thyroid cancer; n: number of patients per category; MTC: medullary thyroid cancer; N: number of patients in the population; RET: rearranged during transfection; SAS: safety analysis set.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

B.2.10.3 Grade 3–4 adverse events

In the *RET*-mutant MTC SAS, Grade 3 or 4 TEAEs were reported [redacted] patients, not taking into account whether these TEAEs were related to selpercatinib treatment (Table 51). The most common Grade 3–4 events were hypertension [redacted], ALT increase (9.0%), hyponatremia [redacted] and AST increase (7.7%).[70]

In the *RET* fusion-positive TC SAS, Grade 3 or 4 TEAEs were reported in [redacted] patients, irrespective of relatedness to selpercatinib, as shown by Table 51. The most common Grade 3–4 TEAEs were hypertension (15.2%), hyponatraemia [redacted] diarrhoea (7.6%) and lymphopenia [redacted].[70]

Table 51: Grade 3–4 TEAEs in 2% or more patients

Preferred term	Incidence, n (%)	
	RET-mutant MTC SAS N=324	*RET* fusion-positive TC SAS N=66
Patients with TEAEs	[redacted]	[redacted]
Hypertension	[redacted]	10 (15.2)
ALT increase	29 (9.0)	[redacted]
Hyponatraemia	[redacted]	[redacted]
AST increase	25 (7.7)	[redacted]
Diarrhoea	22 (6.8)	5 (7.6)

Lymphopenia	[redacted]	[redacted]
ECG QT prolongation	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Abdominal pain	10 (3.1)	3 (4.5)
Hypophosphatemia	[redacted]	[redacted]
Hypocalcaemia	17 (5.2)	[redacted]
Pleural effusion	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Blood alkaline phosphatase increase	[redacted]	[redacted]
Blood creatinine increase	[redacted]	[redacted]
Vomiting	8 (2.5)	2 (3.0)
Weight increase	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECG: electrocardiogram; MTC: medullary thyroid cancer; n: number of patients; RET rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

B.2.10.4 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 is presented in Table 52. Although ALT and AST TEAEs frequently led to withheld doses (ALT:[redacted]; AST:[redacted]) and reductions ([redacted] for both ALT and AST) in the *RET*-mutant MTC SAS, ALT and AST increase led to drug discontinuation in only [redacted] and [redacted], respectively. [redacted] in the *RET*-mutant MTC SAS met the Hy's Law criteria of drug induced liver injury. In the *RET* fusion-positive TC SAS, withheld doses due to ALT and AST increase were observed for [redacted] and [redacted] patients, respectively. Dose reductions for ALT and AST increase were both observed in [redacted] patients, both leading to [redacted] discontinuations. [redacted] patients met Hy's law criteria.

Of the [redacted] patients in the *RET*-mutant MTC SAS, [redacted] patients had a reported history of hypertension and [redacted] did not. The frequency of reported hypertension AEs by any grade was similar between these patients despite the difference in medical history. A minority of

patients in the *RET*-mutant MTC SAS required withheld doses [redacted] and/or reduction [redacted] due to an AE of hypertension; only [redacted] patient [redacted] in the *RET*-mutant MTC SAS discontinued therapy due to an AE of hypertension.

Out of the [redacted] patients in the *RET* fusion-positive TC SAS, [redacted] patients had a history of hypertension and [redacted] did not. Withheld doses and dose reductions took place due to an AE of hypertension in [redacted] patients and [redacted] patients, respectively. [redacted] patients discontinued therapy due to an AE of hypertension in this SAS.

Table 52: ALT/AST and hypertension AESIs in the LIBRETTO-001 trial

Adverse event of special interest, n (%)	*RET*-mutant MTC SAS N=324			*RET* fusion-positive TC SAS N=66		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
AST increase	118 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to study treatment (any grade)	[redacted]			[redacted]		
ALT increase	107 (33.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to study treatment (any grade)	[redacted]			[redacted]		
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to study treatment (any grade)	[redacted]			[redacted]		

Abbreviations: AESI: adverse event of special interest; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MTC: medullary thyroid cancer; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[73] Wirth *et al* (2023).[70]

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 53.

Table 53: Hypersensitivity AESIs in the LIBRETTO-001 trial

Adverse event of special interest	*RET*-mutant MTC SAS N=324	*RET* fusion-positive TC SAS N=66
Drug hypersensitivity, n (%)	[redacted]	[redacted]
Median time to first onset, weeks	[redacted]	[redacted]
Range	[redacted]	[redacted]
Grade 3 hypersensitivity events, n (%)	[redacted]	[redacted]
Grade 4 hypersensitivity events, n (%)	[redacted]	[redacted]

AEs deemed as an 'SAE' attributed to selpercatinib, n (%)	[redacted]	[redacted]
AEs leading to dose modifications, n (%)		
Dose withheld	[redacted]	[redacted]
Dose reduction	[redacted]	[redacted]
Dose discontinuation	[redacted]	[redacted]

Abbreviations: AE: adverse event; AESI: adverse event of special interest; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MTC: medullary thyroid cancer; n: number of patients; SAE: serious adverse event; SAS: safety analysis set.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[73]

Notable event: QT prolongation

Any grade ECG QT prolongation was reported for [redacted] patients in the *RET*-mutant MTC SAS, with [redacted] considered related to selpercatinib. [redacted] experiencing an SAE of ECG QT prolongation was part of the *RET*-mutant MTC SAS. Similarly in the *RET* fusion-positive TC SAS, [redacted] patients experienced an any grade ECG QT prolongation, with [redacted] related to selpercatinib.

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.2.10.5 LIBRETTO-531

A summary of TEAEs in LIBRETTO-531 is presented in Table 54 below. The results demonstrated that selpercatinib was associated with an improved tolerability profile compared to cabozantinib or vandetanib. Overall, 89.6% of patients experienced an AE related to study treatment in the selpercatinib group, compared with 97.9% in the cabozantinib/vandetanib group.[83]

Notably, patients in the cabozantinib/vandetanib group were almost two times more likely to experience Grade 3 or higher AEs that were related to their treatment. Overall, 68.0% of patients in the cabozantinib/vandetanib group experienced a Grade 3 or higher AE related to treatment, compared with 37.3% of patients in the selpercatinib group. Similarly, 5.7% of patients experienced an SAE related to study treatment in the selpercatinib group, compared with 17.5% in the cabozantinib/vandetanib group.[83]

Table 54: Summary of TEAEs in the LIBRETTO-531 trial

	Selpercatinib N=193	Cabozantinib or vandetanib N=97
TEAE, n (%)		
All	186 (96.4)	96 (99.0)
Related to study treatment	173 (89.6)	95 (97.9)

Grade ≥3 TEAE, n (%)		
All	102 (52.8)	74 (76.3)
Related to study treatment	72 (37.3)	66 (68.0)
TEAE leading to permanent treatment discontinuation, n (%)		
All	9 (4.7)	26 (26.8)
Related to study treatment	4 (2.1)	22 (22.7)
TE-SAE, n (%)		
All	42 (21.8)	26 (26.8)
Related to study treatment	11 (5.7)	17 (17.5)
Fatal TEAE, n (%)		
All	4 (2.1)	2 (2.1)
Related to study treatment	1 (0.5)[a]	0 (0.0)

[a] The field of relationship to the trial drug was left blank by the investigator; the relationship was updated to "nonrelated" after the data cutoff date.
Abbreviations: MTC: medullary thyroid cancer; N: number of patients in analysis set; n: number of patients experiencing TEAE; OSAS: overall safety analysis population; RET rearranged during transfection; SAE: serious adverse event; SAS: safety analysis set; TC: thyroid cancer; TEAE: treatment-emergent adverse event.
Source: Hadoux *et al.* (2023)[83]

B.2.11 *Ongoing studies*

The LIBRETTO-001 trial is currently ongoing, however, [redacted]

The Phase III LIBRETTO-531 trial investigating selpercatinib versus standard treatment (cabozantinib or vandetanib) in adult patients with untreated *RET*-mutant MTC is currently ongoing, with an estimated completion date of 2026.[92] Due to the design of the LIBRETTO-531 trial permitting cross-over from the cabozantinib/vandetanib arm into the selpercatinib arm once the PFS endpoint is met, meaning any longer-term OS results will be impacted by treatment-crossover. Further details on LIBRETTO-531 and a summary of the key trial outcomes are presented in Appendix M.

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

Efficacy data from relevant clinical trials for selpercatinib

LIBRETTO-001

The clinical efficacy and safety evidence base for selpercatinib as a treatment for advanced, *RET*-mutant MTC and *RET* fusion-positive TC in patients who have not previously received systemic therapy is informed by the LIBRETTO-001 trial. UK clinical experts during interviews conducted to support this submission confirmed that the population included in LIBRETTO-001 is reflective of patients with advanced *RET*-altered TC and MTC in UK clinical practice.[3]

The clinical efficacy results from LIBRETTO-001 demonstrate that selpercatinib drives clinically meaningful, deep and durable responses in patients with *RET*-mutant MTC and *RET* fusion-positive TC.

At the 13th January 2023 DCO, the primary endpoint in the LIBRETTO-001 trial, ORR, in the cabozantinib/vandetanib naïve *RET*-mutant MTC population was 82.5% ([redacted]143; 95% CI: 75.3, 88.4). Furthermore, 58.7% of patients experienced a PR upon treatment with selpercatinib, along with 23.8% of patients experiencing a CR, demonstrating the efficacy in targeting *RET* in this patient population. Median DOR, PFS and OS were [redacted]; this is due to a low number of events observed despite the long duration of follow-up (39.4 months, 42.4 months and [redacted] months for DOR, PFS and OS, respectively). This long median duration of follow-up for OS in LIBRETTO-001 is broadly similar to those seen in comparator trial publications.[54, 70]

In the systemic therapy naïve *RET* fusion-positive TC population, ORR was 95.8% ([redacted]24; 95% CI: 78.9, 99.9). Furthermore, 75.0% of patients experienced a PR upon treatment with selpercatinib, along with 20.8% of patients experiencing a CR. Median DOR, PFS and OS were also [redacted] (with median follow-up durations of 17.8 months, 24.9 months and [redacted] months for DOR, PFS and OS, respectively).[70]

LIBRETTO-531

Furthermore, results from the LIBRETTO-531 trial, comparing selpercatinib versus cabozantinib/vandetanib in patients with advanced, RET-mutant MTC who had not previously received cabozantinib/vandetanib, provide preliminary data on the comparative efficacy for selpercatinib versus cabozantinib/vandetanib. While data are immature, higher response rates were observed in the selpercatinib treatment arm versus the cabozantinib/vandetanib arm (69.4% and 38.8%, respectively). In LIBRETTO-531, selpercatinib was associated with a stratified PFS HR of 0.28 (95% CI: 0.16, 0.48) versus cabozantinib or vandetanib; in the subgroup analysis of PFS, selpercatinib was associated with a PFS HR of 0.22 (95% CI: 0.11, 0.41) versus cabozantinib specifically, supporting the results of the ITC that indicate selpercatinib substantially reduce the risk of disease progression or death compared to cabozantinib.[83]

Findings from the ITCs

As LIBRETTO-001 is a single-arm trial, ITCs were conducted to provide comparative efficacy evidence on selpercatinib versus the relevant comparators in this indication. Overall, the ITCs conducted to generate comparative efficacy evidence for selpercatinib versus relevant comparators used the best available data and methods outlined in NICE DSU TSD 18.[71]

In the *RET*-mutant MTC patient population, MAICs were conducted to adjust for all identified prognostic variables and treatment effect modifiers that were consistently reported across the LIBRETTO-001 and EXAM trials. The results demonstrate that selpercatinib is associated with a statistically significant treatment benefit for OS and PFS when compared to cabozantinib (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]) and placebo (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). The results versus cabozantinib are consistent with preliminary results from LIBRETTO-531. Importantly, KM OS data were only available for the *RET* M918T-positive subgroup, thus, this subgroup was used as a proxy for the overall *RET*-mutant subgroup when comparing selpercatinib versus cabozantinib.[54] As cabozantinib is known to be more effective in the M918T-positive population than in the overall *RET*-mutant population, the treatment benefit demonstrated in the ITC is likely underestimated.[54, 87]

In the *RET* fusion-positive TC populations, naïve comparisons were necessitated by the differences in trial design, the lack of available data in the comparator trials (for a *RET*-fusion positive patient population) and the small sample sizes relevant to patients with TC in the LIBRETTO-001 trial (n=65, for the any-line population). Comparisons of OS versus BSC were further complicated due to the crossover permitted in both the SELECT and the DECISION trials, for patients receiving placebo.

The ITC results in the TC population demonstrated a statistically significant treatment and clinically meaningful treatment benefit in terms of both OS and PFS for selpercatinib versus lenvatinib (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]), the primary comparator for selpercatinib in UK clinical practice as confirmed by UK clinical experts in TC.[3] Statistically significant and clinically meaningful results were also demonstrated for selpercatinib versus placebo (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]) using the SELECT placebo arm as a proxy. Furthermore, numerical benefits were observed for OS for selpercatinib versus sorafenib (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]), with a statistically significant treatment benefit demonstrated for PFS ([redacted] [95% CI: [redacted], [redacted]; p[redacted]]), though these results should be interpreted with caution due to the clinical plausibility concerns associated with sorafenib OS data. Regardless, sorafenib is not considered a relevant comparator for selpercatinib in this indication.

Safety data on selpercatinib

Overall, the safety profile of selpercatinib is consistent across the overall population enrolled in LIBRETTO-001, the *RET*-mutant MTC population and the *RET* fusion-positive TC population. In the *RET*-mutant MTC SAS and the *RET* fusion-positive TC SAS, Grade 3 or 4 TEAEs were reported by [redacted] and [redacted] patients, respectively, irrespective of relatedness to selpercatinib. Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication.

Overall, selpercatinib was shown to be well tolerated across patient populations and taking into account the clinical efficacy demonstrated in both *RET*-mutant MTC and *RET* fusion-positive TC patients, selpercatinib has demonstrated a positive risk/benefit ratio in these populations.

Early data from LIBRETTO-531 supports the improved safety profile of selpercatinib versus MKIs, specifically cabozantinib; Notably, patients in the cabozantinib/vandetanib group were almost two times more likely to experience Grade 3 or higher AEs that were related to their treatment. Overall, 68.0% of patients in the cabozantinib/vandetanib group experienced a Grade 3 or higher AE related to treatment, compared with 37.3% of patients in the selpercatinib group.[83]

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 for 'people aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy' and for 'people aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)'.
- The model adopted a partitioned survival approach with three health states: PF, PD, and death. The model broadly aligns with the model accepted by the NICE Committee in NICE TA742.[2]
- Stratified and unstratified standard parametric and flexible approaches were used to extrapolate OS and PFS data for selpercatinib (OS, PFS) and relevant comparators.
    - For the *RET*-mutant MTC population, the loglogistic extrapolation was selected to model PFS, for all treatment arms. For OS, the stratified Weibull extrapolation was used to model selpercatinib and BSC; OS for cabozantinib was modelled by applying the HR for cabozantinib versus placebo from EXAM to the BSC extrapolation
    - For the *RET* fusion-positive TC population, the piecewise exponential extrapolation and the stratified Weibull extrapolation were selected to model OS and PFS, respectively, for all treatment arms.
    - In both populations, TTD for all comparators was assumed equal to PFS. For selpercatinib treatment, an additional delay was included to represent the time between disease progression and treatment discontinuation based on LIBRETTO-001 ([redacted] weeks for *RET*-mutant MTC and [redacted] weeks for *RET* fusion-positive TC).
- Utility values for the PF and PD health states (for both MTC and TC populations) were derived from Fordham et al. (2015),[93] in line with previous technology appraisals (TA516 and TA535).[24, 25]
- Resource use and costs included in the model were based on information from the LIBRETTO-001 trial, previous technology appraisals (TA516 and TA535) and appropriate published sources including the BNF and NHS Reference Costs (2021/22).[24, 25]
- Feedback from UK clinicians was sought in order to validate assumptions and inputs included in the model.[3]

Comparators

- For patients with *RET*-mutant MTC, selpercatinib was compared to cabozantinib and BSC via a MAIC using data from the LIBRETTO-001 trial for selpercatinib survival inputs, and the EXAM trial for comparator therapies.[54, 88]
- For patients with *RET* fusion-positive TC, selpercatinib was compared to lenvatinib and BSC via a naïve ITC using data from the LIBRETTO-001 trial for selpercatinib survival inputs and the SELECT trial for lenvatinib and BSC.[89]
- Whilst efficacy data for selpercatinib are available for the systemic therapy naïve analysis set (TC) and the cabozantinib/vandetanib naïve analysis set (MTC) from LIBRETTO-001, combined data from the any-line TC and MTC populations were used to more closely align with the comparator populations. As such, combined efficacy data for the treatment naïve and pre-treated patients in the LIBRETTO-001 trial were used as a proxy to determine the cost-effectiveness of selpercatinib in the indications of interest in this submission.

Base case cost-effectiveness results

- For advanced *RET*-mutant MTC, under the base case assumptions and with the confidential PAS discount of [redacted] provided with this submission, selpercatinib was associated with pairwise

ICERs of £29,738 and £40,184 per quality-adjusted life year (QALY) gained versus cabozantinib and BSC, respectively.

- For advanced *RET*-fusion TC selpercatinib was associated with an ICER of £34,620 per QALY gained versus lenvatinib and £43,067 per QALY gained versus BSC, respectively.

Sensitivity and scenario analyses

- The results of the sensitivity analyses demonstrated that the model is robust to parameter uncertainty. The most influential parameters identified in the DSA were the discount rate for outcomes and costs, and the progression-free health state utility value and costs.
- Scenario analyses demonstrated that there is minimal uncertainty surrounding the results of the base case cost-effectiveness results. A number of plausible scenarios decreased the base case ICERs, while the ICER increased by no more than £5,000/QALY across all scenarios considered.

Conclusions

- The results of the economic analysis demonstrate that selpercatinib would introduce substantial QALY benefits compared to the current treatments for TC and MTC in UK clinical practice, and would provide an effective treatment option for patients who currently face a poor prognosis and have a high unmet need.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted in September 2019 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 H.

As TC and MTC are rare types of cancer and there are no other selective *RET* kinase inhibitors currently available to patients who have not previously received systemic therapy for advanced disease, 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.

Three appraisals were identified that are relevant to this submission – in addition to these, two appraisals in thyroid cancer indications have also subsequently been published:

- Cabozantinib for treating MTC (TA516)[24]
- Vandetanib for treating MTC (TA550)[65]
- Lenvatinib and sorafenib for treating DTC after radioactive iodine (TA535)[25]
- Selpercatinib for treating advanced *RET*-mutant MTC and *RET*-fusion positive TC (TA742)[2]
- Cabozantinib for previously treated differentiated TC (ID4046)[28]

Of these, TA550 and ID4046 were considered less relevant to this appraisal because they received negative recommendations. A summary of the two most relevant appraisals which considered populations of patients who had not previously received systemic therapy, TA516 and TA535, can be found in Table 55.

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 in adults whose disease does not respond to radioactive iodine.

Table 55: 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; CUA: cost-utility analysis; EGFR: epidermal growth factor receptor; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; NR: not reported; RR-DTC: radioactive iodine refractory differentiated thyroid cancer; VEGF/VEGFR: vascular endothelial growth factor/vascular endothelial growth factor receptor.
Source: NICE TA516,[24] NICE TA535.[25]

B.3.2 *Economic analysis*

The objective of this economic analysis was to assess the cost effectiveness of selpercatinib as a treatment for patients with advanced *RET*-mutant MTC and advanced *RET* fusion-positive TC who have not previously received systemic therapy for advanced disease.

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 economic analyses considered the following populations:

- People aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)
- People aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)

These populations reflect the anticipated positioning of selpercatinib in the treatment pathway, as confirmed by UK clinical experts as part of this appraisal.[3]

As set out in the decision problem in Section B.1.1, the *RET*-mutant MTC population of interest in this submission is narrower than the technology's full marketing authorisation for selpercatinib "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy".

The MTC population considered in the economic model was the pooled, any-line MTC patient population (n=295) in the LIBRETTO-001 trial, comprised of the MTC: Cab/Van analysis set (n=152; patients with MTC who had received 1 or more lines of prior cabozantinib or vandetanib) and the Cab/VanNaïve analysis set (n=143; patients with MTC who were naïve to cabozantinib and/or vandetanib).[70, 75] As discussed in Section B.2.9, data from the two efficacy analysis sets were pooled in the ITCs and subsequently in the economic analysis in order to align with the available data from the EXAM trial for cabozantinib.[54]

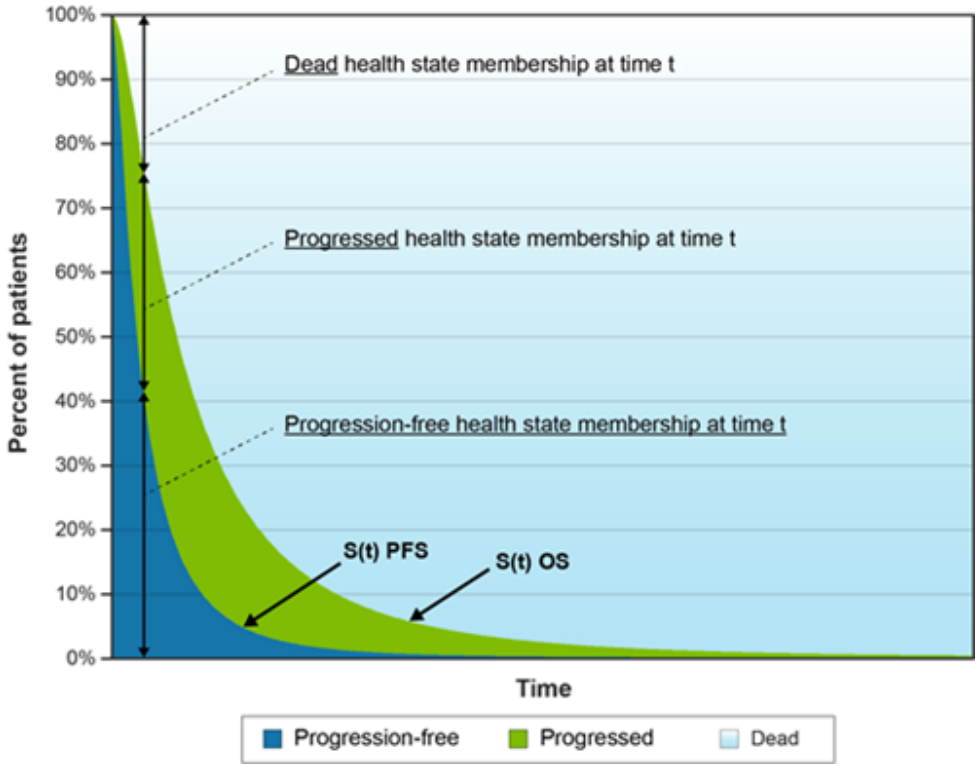
The *RET* fusion-positive TC population of relevance to this submission is also narrower than the technology's full anticipated marketing authorisation for selpercatinib [redacted]

The population considered in the economic analysis was the any-line TC population (n=65) comprised of patients with TC in the LIBRETTO-001 trial who were systemic therapy naïve (with the exception of radioactive iodine therapy, Section B.1.3.1) (n=24) or patients with TC that had previously received systemic therapy (n=41).[70, 75] As discussed in Section B.2.9, this any-line population was used to inform efficacy of selpercatinib in *RET* fusion-positive TC patients in the model in order to align with the available data from the SELECT trial for lenvatinib.

B.3.2.2 Model structure

A *de novo* economic model was developed in Microsoft Excel to evaluate the cost-effectiveness of selpercatinib versus relevant comparators in the populations of interest to this submission. A cohort-based PSM was developed, consisting of three mutually exclusive health states: progression free (PF), progressed disease (PF) and death. A graphical depiction of the partitioned survival model (PSM) structure is presented in Figure 35.

Figure 35: 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 approach was selected as it allows for modelling of OS and PFS based on study-observed events, which facilitates the replication of within-trial data and allows the clinical benefits of selpercatinib versus the relevant comparators to be captured by reflecting the increased proportion of patients expected to be alive/progression-free over time. Importantly, the PFS and OS curves can be constructed from summary KM data in the absence of individual 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. Furthermore, the use of a PSM aligns with previous NICE appraisals in TC and MTC (such as, TA516, TA535 and TA742).[2, 24, 25]

As discussed above, the PSM comprises the three mutually exclusive health states of PF, PD and death. Cohorts of people with advanced *RET*-mutant MTC and *RET* fusion-positive TC who require systemic therapy were modelled to enter the 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 the 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 associated with treatment acquisition, treatment administration, medical monitoring and costs to manage Grade 3–4 adverse events while in this state. Patients experience higher utility compared to progressed disease and 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 incur health state costs and costs associated with PD following progression (as detailed in Section B.3.5.2). The PD health state is associated with lower utility compared with the PF health state, 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 the OS curve). This is an absorbing state and a cost associated with palliative care is applied as a one-off cost 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, and the death health state is an absorbing health state.

Features of the *de novo* analysis

The economic analysis for this evaluation was compared to previous NICE evaluations in advanced TC and MTC. Table 56 summarises the features of the economic analyses used in prior appraisals for MTC and TC for patients who have not previously received systemic therapy for advanced disease (TA516 and TA535), as well as the model utilised for the previous selpercatinib appraisal (TA742), with justification provided on the approach taken for the current analysis.[2, 24, 25]

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 that were considered in the model included: drug acquisition costs for selpercatinib and comparators and associated drug administration costs, AE costs, subsequent treatments, other resource use costs (by health state) and the 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 PSS costs, over a lifetime time horizon of the patient cohort from the initiation of treatment.

Considering the mean age at model entry for the MTC and TC populations ([redacted] years and [redacted] years, respectively), a time horizon of 25 years was used in the base case to represent a lifetime horizon. A weekly cycle length was considered in the base case, and both costs and effects were discounted at 3.5% annually, in line with the NICE reference case.[94]

The economic analysis is conducted using the most recent estimates of resource use and treatment costs available from NHS Reference Costs (2021/22) and published sources (2022/23). Costs based on previous cost-years or in other currencies are inflated to the model cost-year (2023) using the Consumer Prices Health Index [95] and/or converted to UK, as applicable.

Table 56: Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA516	TA535	TA742	Chosen values	Justification
Model structure	Partitioned survival model	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)	Lifetime horizon (Lenvatinib: 33.35 years; sorafenib: 30 years)	Lifetime horizon (25 years)	Lifetime horizon (25 years)	NICE reference case[94]
Cycle length	1 month (28 days) and half cycle correction	1 month (28 days) and half cycle correction	Weekly	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%	3.5%	NICE reference case[94]
Source of utilities	Fordham *et al.* (2015)[93] PF state: 0.80 PD state: 0.50 Disutility AEs: −0.11	Fordham *et al.* (2015)[93], DECISION trial[90] **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	Fordham *et al.* (2015)[93] PF state: 0.80 PD state: 0.50 Disutility AEs: −0.11	Fordham *et al.* (2015)[93] PF state: 0.80 PD state: 0.50 Disutility AEs: Various (Table 82 and Table 83)	Health-state utility estimates reported by Fordham et al. (2015)[93] were accepted by the NICE appraisal committee in TA516, TA535 and TA742.[2, 24, 25] While EORTC QLQ-C30 data were collected in the LIBRETTO-001 study for patients with *RET*-mutant MTC and *RET*-fusion positive TC, mapping of these data to EQ-5D resulted in highly implausible mean utilities (Section B.3.4.2), in line with the findings during NICE TA742.[1] Given this, and that no novel utility data were identified as part of the SLRs, the use of utilities from Fordham *et al.* (2015)[93] was considered to represent the most appropriate

		Sorafenib SD state: 0.68 Responsive state: 0.74 Progressive state: 0.64			approach, in line with precedent from previous appraisals.
Source of costs	NHS Reference Costs PSSRU BNF	NHS Reference Costs PSSRU BNF	NHS Reference Costs Collection PSSRU BNF	NHS Reference Costs Collection PSSRU BNF	Established sources of costs within the NHS. In line with the NICE reference case previous appraisals[24, 25, 94]
Resource use	Expert opinion	Expert opinion	Resource use was derived from prior appraisals[24, 25]	Resource use was derived from prior appraisals[24, 25]	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	QALYs	NICE reference case[94]

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

Intervention

The intervention of interest is selpercatinib administered orally twice daily (BID) in 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation. The selpercatinib dose included in the economic model is 160 mg orally BID, reflecting the dose for adult and adolescent patients weighing ≥ 50 kg, in line with median patient weights in LIBRETTO-001 of [redacted] kg and [redacted] kg in the any-line *RET*-mutant MTC and *RET*-fusion positive TC populations, respectively. As such, the use of the 160 mg oral BID daily dose of selpercatinib is in line with the RP2D of the LIBRETTO-001 trial supporting the submission and the SmPC for selpercatinib.[1]

The economic model also accounts for patients who require dose reductions whilst receiving selpercatinib (as detailed in Section B.3.5.1) – the selpercatinib SmPC specifies that the dose of selpercatinib is reduced by 40 mg per day for each dose reduction, resulting in doses of 120 mg BID, 80 mg BID and 40 mg BID for first, second and third dose reductions, respectively.[1]

Comparators: RET-mutant MTC

In line with standard care in UK clinical practice, the comparators included in the model for the *RET*-mutant MTC population were cabozantinib and BSC (Section B.1.1). As part of this appraisal, UK clinical experts indicated that cabozantinib is predominantly used for most patients in clinical practice, with only 10-20% of patients receiving BSC, consisting of adolescent patients or patients otherwise ineligible to receive cabozantinib.[3]

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 – this is modelled as one 80 mg capsule and three 20 mg grey capsules.[88, 96] The economic model also accounts for patients who require dose reductions whilst receiving cabozantinib (as detailed in Section B.3.5.1); the cabozantinib SmPC specifies that cabozantinib should be reduced to 100 mg daily and then 60 mg daily upon first and second dose reductions, respectively.[97]

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.[24]

Comparators: *RET*-fusion positive TC

In line with standard care in UK clinical practice, the comparators included in the model for the *RET* fusion-positive TC population were lenvatinib and BSC (Section B.1.1). As part of this appraisal, UK clinical experts indicated that lenvatinib is predominantly used in clinical practice, with the majority of the remaining patients receiving BSC (approximately 10% of patients).[3] Of all patients that receive MKIs, approximately 90–95% were estimated to receive lenvatinib, with the remaining minority of patients receiving sorafenib; as such, sorafenib is not considered a relevant comparator for selpercatinib in this appraisal and was not included in the economic model.[3]

The dose for lenvatinib included in the model was 24 mg orally once daily until the occurrence of unacceptable toxic effects or disease progression, in line with its licensed indication for its use in DTC and the Phase III SELECT trial.[89, 98] The economic model also accounts for patients who require dose reductions when receiving lenvatinib (as detailed in Section B.3.5.1) – the lenvatinib SmPC specifies dose reductions to 20 mg, 14 mg and 10 mg daily upon first, second and third dose reductions, respectively.[99]

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 discussed in Section B.2.9, the placebo arm in the SELECT trial for lenvatinib was considered to represent a suitable proxy for BSC; this is aligned with TA535 and TA742.[2, 25] 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 arms of either trials were 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*

Clinical data for selpercatinib for *RET*-mutant MTC and *RET* fusion-positive TC were derived from the relevant populations of the LIBRETTO-001 trial, as outlined in Section B.3.2.1.[73, 100] For cabozantinib and BSC, clinical data in *RET*-mutant MTC were derived from the EXAM trial.[54, 87, 88] For the relevant comparators in TC, clinical data in *RET*-fusion positive TC were derived from the SELECT trial for lenvatinib and BSC.[89]

RET-mutant MTC

As discussed in Section B.2.9, an unanchored MAIC was conducted using the any-line MTC population from the LIBRETTO-001 trial (MTC: Cab/Van and MTC: Cab/VanNaïve; n=295 in total)[75] and summary evidence from the EXAM trial, as reported in Schlumberger et al. (2017) and Sherman et al. (2016).[54, 87] The any-line pooled population from the LIBRETT0-001 trial was used rather than the cabozantinib/vandetanib naïve analysis set (MTC: Cab/VanNaïve) because the former more closely matches the characteristics of the EXAM trial population, and provides a larger patient-level data set. 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).

A summary of the clinical evidence sources informing parameters for selpercatinib and comparators for patients with *RET*-mutant MTC in the economic model is provided in Table 57.

As outlined in Section B.2.9, no OS KM data were available from the EXAM trial for the *RET*-mutant subgroup, specifically. However, OS KM data were available for the *RET* M918T-positive subgroup of the EXAM trial (cabozantinib, n=81; placebo, n=45).[54] As part of TA742, UK 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, extrapolation of the OS KM data 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.[54]

The OS KM data for cabozantinib from the *RET* M918T-positive subgroup of the EXAM trial was not considered generalisable to the *RET*-mutant patient population of interest to this appraisal,

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 (0.15 [95% CI: 0.08, 0.28] versus 0.23 [95% CI: 0.14, 0.38]).[54, 87] As such, OS for cabozantinib in the model was estimated by applying the HR for cabozantinib versus placebo in the *RET*-mutant subgroup to the chosen OS curve for placebo.

Table 57: Summary of clinical evidence sources informing parameters for selpercatinib and comparators in the economic model (RET-mutant MTC population)

Clinical parameter	Intervention and comparators		
	Selpercatinib[70, 75]	Cabozantinib	BSC
Baseline characteristics	• LIBRETTO-001 any-line MTC population (MTC: Cab/Van and MTC: Cab/VanNaïve; n=295)		
PFS	• Propensity score-weighted KM data for the LIBRETTO-001 any-line population (MTC: Cab/Van and MTC: Cab/VanNaïve; n=295) • Matched to baseline characteristics of the *RET*-mutant population receiving cabozantinib in the EXAM trial	• Unweighted KM data for the *RET*-mutant subgroup receiving cabozantinib (n=107) in the EXAM trial, from Sherman et al. (2016)[87]	• Unweighted KM data for the *RET*-mutant subgroup receiving placebo (n=62) in the EXAM trial, from Sherman *et al.* (2016) [87]
OS	• Propensity score-weighted KM data for the LIBRETTO-001 any-line population (MTC: Cab/Van and MTC: Cab/VanNaïve; n=295) • 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 from Sherman et al. (2016)[87] applied to the OS curve 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)[54]
Time-on-treatment	• Assumed equal to PFS with an additional delay based on the delay between disease progression and treatment discontinuation observed in the RET-mutant MTC population in LIBRETTO-001 ([redacted] weeks)	• Assumed equal to PFS	NA
AEs	• LIBRETTO-001 MTC SAS (n=324)	• Cabozantinib arm of the EXAM trial (n=214), from Elisei *et al.* (2013)[88]	• Placebo arm of the EXAM trial (n=109), from Elisei *et al.* (2013)[88]

Abbreviations: AEs: adverse events; BSC: best supportive care; Cab: cabozantinib; KM: Kaplan-Meier; MTC: medullary thyroid cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection; SAS: safety analysis set; Van: vandetanib.

RET fusion-positive TC

As outlined in Section B.2.9, a naïve indirect comparison was performed using data from the any-line *RET* fusion-positive TC patient population in the LIBRETTO-001 trial (n=65) for selpercatinib and the SELECT trial for lenvatinib and placebo (as a proxy for BSC). As discussed in Section B.2.9, placebo from the SELECT trial was considered the most suitable proxy for BSC, due to the availability of crossover adjusted OS KM data for placebo in the SELECT trial. This is aligned with the approaches used in TA535 and TA742.[2, 25]

The clinical evidence sources informing parameters for selpercatinib and comparators for patients with *RET* fusion-positive TC in the economic model are summarised in Table 58. KM data for 131 patients who received placebo from the SELECT ITT population (Section B.2.9) 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.

Table 58: Summary of clinical evidence sources informing parameters for selpercatinib and comparators in the economic model (*RET* fusion-positive TC population)

Clinical parameter	Intervention and comparators		
	Selpercatinib[70, 75]	Lenvatinib	BSC
Baseline characteristics	LIBRETTO-001 TC any-line population (n=65)[a, b]		
PFS	• KM data for LIBRETTO-001 any-line population (n=65)	• KM data for the ITT population receiving lenvatinib (n=261) in SELECT, from Schlumberger et al. (2015)[89]	• KM data for the ITT population receiving placebo (n=131) in SELECT, from Schlumberger *et al.* (2015)[89]
OS	• KM data for LIBRETTO-001 any-line population (n=65)	• RPSFT-adjusted KM data for patients receiving lenvatinib (n=261) in the ITT population of SELECT, from NICE TA535[25]	• RPSFT-adjusted KM data for patients receiving placebo (n=131) in the ITT population of SELECT, from NICE TA535[25]
Time-on-treatment	• Assumed equal to PFS with an additional delay based on the delay between disease progression and treatment discontinuation observed in the RET fusion-positive TC population in LIBRETTO-001 ([redacted] weeks)	• Assumed equal to PFS	• NA
AEs	• LIBRETTO-001 TC safety analysis set (n=66)	• Lenvatinib arm of the SELECT trial (n=261); Schlumberger *et al.* (2015)[89]	• Placebo arm of the SELECT trial (n=131); Schlumberger *et al.* (2015)[89]

[a] Comprised of the 'TC: TrtSysNaïve' analysis set (N=24) and the 'TC: TrtSys' (systemic therapy experienced patients with TC) analysis set (N=41). [b] Patients had a variety of TCs, including PTC: [redacted]; poorly differentiated TC: [redacted]; anaplastic TC; [redacted]; Hürthle cell thyroid cancer: [redacted].
Abbreviations: AEs: adverse events; BSC: best supportive care; 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; thyroid cancer.

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohort are provided in Table 59. 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 any-line *RET* fusion-positive TC populations from the LIBRETTO-001 trial for the MTC and TC populations, respectively.

Table 59: Patient characteristics in the model

Model parameter	Value	Source
***RET*-mutant MTC**		
Mean age (SD)	[redacted]	LIBRETTO-001 any-line population (MTC: Cab/Van and MTC: Cab/Van Naïve; n=295)
Sex (% female)	39.0%	
***RET* fusion-positive TC**		
Mean age (SD)	[redacted]	LIBRETTO-001 any-line population (any-line population; n=65)
Sex (% female)	50.8%	

Abbreviations: MTC: medullary thyroid cancer; *RET*: rearranged during transfection; SD: standard deviation; TC: thyroid cancer.
Source: Lilly data on file,[73] Raez *et al* (2023).[75]

B.3.3.2 Survival inputs and assumptions

As described in Section B.3.2.2, the model is a cohort-based PSM consisting of three mutually exclusive health states: PF, PD, and death. The proportion of patients in each heath state at each weekly model cycle was 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,[100] EXAM,[54, 87, 88] and SELECT[25, 89]) were shorter than the model time horizon (Section B.3.2.2), extrapolation from the observed OS and PFS data was required.

For the purposes of survival analysis for the comparators, pseudo patient-level data was derived from the published KM curves and number of event information from the EXAM and SELECT and trials using the algorithm described by Guyot *et al.* 2012.[101]

In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance, 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.[102] For the spline models, these were developed based on the algorithm by Royston and Parmar *et al.* (2002).[103] 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 proportional hazards (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:[102]

- The statistical fit of the models to the trial data, based on AIC and BIC goodness-of-fit statistics. Tests for the PH assumption between treatment arms were conducted to determine the most appropriate models for consideration
- Goodness of fit of the models to the trial data was also assessed based on visual inspection against the observed KM curves
- Clinical plausibility for both short-term and long-term estimates of survival was assessed, based on feedback from UK clinical experts and published information from TA516 and TA535 for comparator therapies, and TA742 for selpercatinib [2, 24, 25]
    - Feedback from UK clinical experts was gathered as part of this appraisal during teleconference interviews to determine plausible long-term estimates of PFS and OS for selpercatinib and each relevant comparator. When models were being selected to extrapolation immature survival data, these estimates of plausible long-term survival were used to inform the most appropriate extrapolation

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).

B.3.3.3 Time-to-event analyses: *RET*-mutant MTC

Progression-free survival

As described in Section B.3.3.2, 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=107) in the EXAM trial.

The AIC and BIC values for each survival model are presented in Table 60, and the long-term extrapolations of PFS are presented in Figure 36–Figure 38. Table 61–Table 63 present the corresponding median and landmark PFS estimates (at 5, 10 and 20 years). The results of proportional hazards assessments for selpercatinib versus cabozantinib and BSC in the *RET*-mutant are presented in Appendix O.1.

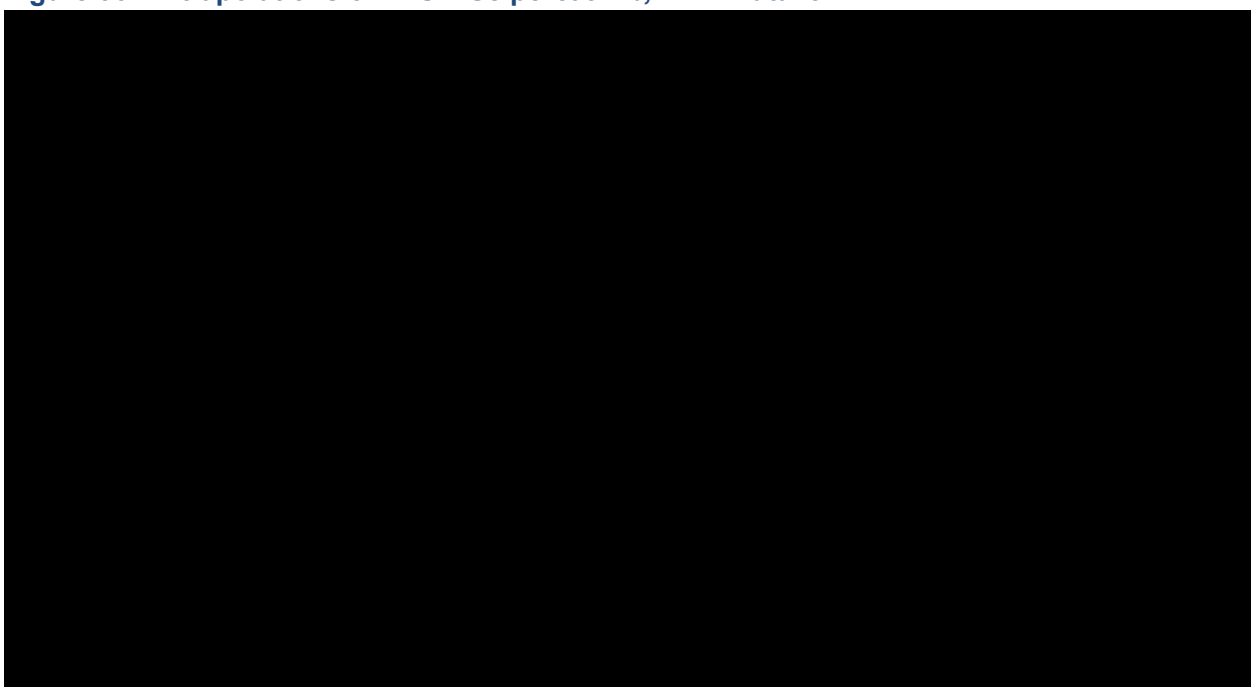
Table 60: Summary of goodness-of-fit data for stratified models for progression-free survival for selpercatinib, cabozantinib and BSC in *RET*-mutant MTC

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]
Generalised gamma[a]	[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]
Stratified generalised gamma[b]	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. [a] The generalised gamma extrapolation did not converge. [b] The stratified generalised gamma extrapolation did not converge for cabozantinib only.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BSC: best supportive care; MTC: medullary thyroid cancer.

Figure 36: Extrapolations of PFS – Selpercatinib, *RET*-mutant MTC



Abbreviations: MTC: medullary thyroid cancer; PFS: progression-free survival; Prop: proportion; PFS: progression free survival; RET: rearranged during transfection.

Table 61: Median and landmark rate estimates of PFS for selpercatinib in *RET*-mutant MTC

Parametric curve	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	[redacted]	[redacted]	[redacted]	[redacted]
Median and landmark survival for each extrapolation				
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma[a]	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival. [a] The generalised gamma extrapolation did not converge.
Abbreviations: MTC: medullary thyroid cancer; NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection.

Figure 37: Extrapolations of PFS – Cabozantinib, RET-mutant MTC

Abbreviations: MTC: medullary thyroid cancer; PFS: progression free survival; Prop: proportion; RET: rearranged during transfection.

Table 62: Median and landmark rate estimates of PFS for cabozantinib in *RET*-mutant MTC

Parametric curve	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	5–30	0–5	0
Median and landmark survival for each extrapolation				
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[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 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]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised Gamma[b]	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival. [a] The generalised gamma extrapolation did not converge. [b] The stratified generalised gamma extrapolation did not converge for cabozantinib only.
Abbreviations: MTC: medullary thyroid cancer; NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection.

Figure 38: Extrapolations of PFS – BSC, *RET*-mutant MTC

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; PFS: progression free survival; Prop: proportion; *RET*: rearranged during transfection.

Table 63: Median and landmark rate estimates of PFS for BSC in *RET*-mutant MTC

Parametric curve	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	[redacted]	[redacted]	[redacted]	[redacted]
Median and landmark survival for each extrapolation				
Stratified spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[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 lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival. [a] The generalised gamma extrapolation did not converge.
Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection.

Based on AIC/BIC criteria, the stratified Weibull and stratified 2-knot spline show the best statistical fit, followed by the stratified Gompertz and the stratified 3-knot spline. Given the relatively similar statistical fit across all models, and the relatively high number of patients still progression-free at the time of the latest DCO of LIBRETTO-001 (13th January 2023), clinical plausibility was considered to represent the most important factor in curve selection.

To support this appraisal, UK clinical experts provided estimates of the proportion of patients anticipated to be progression-free following treatment with each treatment at landmark timepoints. Based on these estimates, the loglogistic extrapolation was selected to model PFS for selpercatinib, cabozantinib and BSC. This also aligns with the preferences of the Committee in a previous appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742), which was based on an earlier data cut of the same analysis sets of LIBRETTO-001 used to inform the efficacy of selpercatinib and BSC in this appraisal.[2]

NICE DSU recommends that where parametric models are fitted separately to individual treatment arms the same 'type' of model (i.e., the same parametric family) should be used unless justified by clinical judgement, biological plausibility, and robust statistical analysis; as such, the same parametric model (loglogistic) was selected to model PFS for all treatment arms in the base case economic analysis. The gamma and spline knot 1 extrapolations were explored in scenario analyses.

Overall survival

Information related to the assessment of the PH assumption for OS is presented in Appendix O. 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) and cabozantinib (n=81) in the EXAM trial. As outlined in B.3.3, OS for cabozantinib is modelled by applying the HR for cabozantinib versus placebo (a proxy for BSC) from EXAM to the BSC extrapolation. As such, parametric extrapolations for OS were limited to those that were consistent with the PH assumption.

Table 64 summarises the AIC and BIC values for each survival model, and the long-term extrapolations of OS are presented in Figure 39–Figure 41. Table 65–Table 67 present the corresponding median and landmark OS estimates (at 5, 10 and 20 years).

Table 64: Summary of goodness-of-fit data for selpercatinib, cabozantinib and BSC OS 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]
Generalised gamma	[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]
Stratified generalised gamma	[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; OS: overall survival.

Figure 39: Extrapolations of OS – Selpercatinib, *RET*-mutant MTC

Abbreviations: MTC: medullary thyroid cancer; OS: overall survival; Prop: proportion; *RET*: rearranged during transfection.

Table 65: Median and landmark rate estimates of OS for selpercatinib in *RET*-mutant MTC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	[redacted]	[redacted]	[redacted]
Median and landmark survival for each extrapolation				
Stratified spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: MTC: medullary thyroid cancer; OS: overall survival; RET: rearranged during transfection.

Figure 40: Extrapolation of OS – Cabozantinib, *RET*-mutant MTC

The OS extrapolation for cabozantinib was derived from the HR versus placebo (BSC).[54]
Abbreviations: MTC: medullary thyroid cancer; OS: overall survival; Prop: proportion; *RET*: rearranged during transfection.

Table 66: Median and landmark rate estimates of OS for cabozantinib in *RET*-mutant MTC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	[redacted]	[redacted]	[redacted]
Median and landmark survival for each extrapolation				
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified 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]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival. Parametric curves were limited to those that were consistent with the PH assumption, as cabozantinib OS is modelled via the application of a HR to the BSC extrapolation.
Abbreviations: MTC: medullary thyroid cancer; NA: not applicable; OS: overall survival; RET: rearranged during transfection.

Figure 41: Extrapolations of OS – BSC, *RET*-mutant MTC

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; OS: overall survival; Prop: proportion; *RET*: rearranged during transfection.

Table 67: Median and landmark rate estimates of OS for BSC in RET-mutant MTC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	[redacted]	[redacted]	[redacted]
Median and landmark survival for each extrapolation				
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[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 gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; NA: not applicable; OS: overall survival; RET: rearranged during transfection.

Based on AIC/BIC criteria, the loglogistic and exponential extrapolations show the best statistical fit to the observed OS KM data. However, there are minimal differences in AIC/BIC criteria for all extrapolations, suggesting that all extrapolations explored show a similar goodness-of-fit to the observed data. Both the loglogistic and exponential extrapolations overestimate OS for selpercatinib, and the loglogistic extrapolation is not suitable considering the requirement to satisfy the PH assumption due to modelling cabozantinib OS via a HR.

As outlined above, to support this appraisal, UK clinical experts provided estimates of the proportion of patients anticipated to be alive following treatment with each treatment at landmark timepoints. Based on these estimates, the stratified Weibull extrapolation was selected to model OS for selpercatinib and BSC (with cabozantinib modelled via a HR, as detailed below); as the most pessimistic OS curve for selpercatinib, the stratified Weibull aligns most closely with the estimates provided by the UK clinical experts. This also aligns with the preferences of the Committee in a previous appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742), which was based on an earlier data cut of the same analysis sets of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal.[2]

As outlined above, NICE DSU recommends that where parametric models are fitted separately to individual treatment arms the same 'type' of model (i.e., the same parametric family) should be used unless justified by clinical judgement, biological plausibility, and robust statistical analysis; as such, the same parametric model (stratified Weibull) was selected to model OS for all treatment arms.

Based on the stratified Weibull extrapolation, a proportion of patients in the selpercatinib arm are assumed to be alive at the end of the model time horizon; however, it is assumed that no further benefits are accrued after 25 years, thereby decreasing any uncertainty associated with the long-term extrapolation of selpercatinib OS.

The stratified gamma extrapolation was explored in a scenario analysis.

OS for cabozantinib

As outlined in Section B.3.3.2, OS KM data for cabozantinib from the *RET* M918T-positive subgroup of the EXAM trial were 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. Therefore, 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 health economic modelling in oncology and was used for PFS by the Assessment Group (AG) in the appraisal of cabozantinib (TA516).[24] The HRs reported for the *RET*-mutant subgroup of the EXAM trial and used in the cost-effectiveness analysis are presented in Table 68. The large discrepancy in PFS and OS HRs for cabozantinib versus placebo are likely due to the permitting of cross-over from the placebo arm to the cabozantinib arm in the EXAM trial.

Table 68: 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[54]

[a] Not used in the model because KM 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.

B.3.3.4 *Time-to-event analyses: RET* fusion-positive TC

Progression-free survival

Information related to the assessment of the PH assumption for PFS is presented in Appendix O. A range of stratified parametric functions were fitted to the PFS KM data for the any-line TC population from LIBRETTO-001 and the PFS KM data for the SELECT ITT population receiving lenvatinib (n=261) and BSC (n=131).

Table 69 summarises the AIC and BIC values for the best-fitting survival models, and the long-term extrapolations of PFS are presented in Figure 42, Figure 43 and Figure 44 for selpercatinib, lenvatinib and BSC, respectively. Table 70, Table 71 and Table 72 present the corresponding median and landmark PFS estimates (at 5, 10 and 20 years) for selpercatinib, lenvatinib and BSC, respectively.

Table 69: Summary of goodness-of-fit data for selpercatinib, lenvatinib and BSC PFS in *RET* fusion-positive TC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
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]
Generalised gamma	[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]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential	[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; NA: not applicable; PFS: progression free survival; RET: rearranged during transfection; TC: thyroid cancer.

Figure 42: Extrapolations of PFS – Selpercatinib, *RET* fusion-positive TC

[redacted]

Abbreviations: PFS: progression free survival; Prop: proportion; RET: rearranged during transfection; TC: thyroid cancer.

Table 70: Median and landmark rate estimates of PFS for selpercatinib in *RET* fusion-positive TC

Parametric curve	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	[redacted]	[redacted]	[redacted]
Median and landmark survival for each extrapolation				
Stratified spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]

Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.

Figure 43: Extrapolations of PFS – Lenvatinib, *RET* fusion-positive TC

Abbreviations: PFS: progression free survival; Prop: proportion; *RET*: rearranged during transfection; TC: thyroid cancer.

Table 71: Median and landmark rate estimates of PFS for lenvatinib in *RET* fusion-positive TC

Parametric Curve	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	5–10	0–2	0–1
Median and landmark survival for each extrapolation				
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.

Figure 44: Extrapolations of PFS – BSC *RET* fusion-positive TC

Abbreviations: BSC: best supportive care; PFS: progression free survival; Prop: proportion; RET: rearranged during transfection; TC: thyroid cancer.

Table 72: Median and landmark rate estimates of PFS for BSC in *RET* fusion-positive TC

Parametric Curve	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	0	0	0
Median and landmark survival for each extrapolation				
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[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 Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: BSC: best supportive care; PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.

In TA535, results from the Assessment Group analyses showed that, within the SELECT trial, the PH assumption did not hold for the majority of survival outcomes.[25] Consequently, stratified survival models were fitted. Whilst unstratified models were also fitted for completeness, stratified models were deemed more appropriate.

Based on AIC/BIC criteria, the 3-knot spline extrapolation shows the best statistical fit to the observed PFS KM data. However, all extrapolations demonstrate similar AIC/BIC criteria,

suggesting that they have a similar goodness-of-fit to the observed data. Due to the similar statistical fit of all extrapolations, clinical plausibility (in terms of plausible landmark PFS rates) were prioritised for decision making. In addition, considering the long-term estimates produced by this model and estimates of PFS for patients receiving selpercatinib, lenvatinib and BSC from UK clinical experts, the 3-knot spline model appears to overestimate PFS for selpercatinib and lenvatinib.

As outlined previously, to support this appraisal, UK clinical experts provided estimates of the proportion of patients anticipated to be progression-free following treatment with each treatment at landmark timepoints. Based on these estimates, and to align with the preferences of the Committee in TA742, the stratified Weibull extrapolation was selected to model PFS for selpercatinib, lenvatinib and BSC; the selection of the same extrapolation to model PFS for all treatment arms is in line with guidance from NICE DSU.[8]

The selection of the stratified Weibull curve also aligns with the preferences of the Committee in a previous appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742), which was based on an earlier data cut of the same analysis sets of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal.[2]

The exponential extrapolation was explored in a scenario analysis.

Overall survival

Information related to the assessment of the PH assumption for OS is presented in Appendix O. A range of parametric functions were fitted to OS data available for the any-line *RET* fusion-positive TC patients in LIBRETTO-001 and the RPSFT-adjusted OS curve for lenvatinib and placebo from the SELECT trial.

Table 73 summarises the AIC and BIC values for each survival models, and the long-term extrapolations of OS are presented in Figure 45, Figure 46 and Figure 47 for selpercatinib. lenvatinib and BSC, respectively. Table 74, Table 75 and Table 76 present the corresponding median and landmark OS estimates (at 3, 5, 10 and 20 years) for selpercatinib, lenvatinib and BSC, respectively.

Table 73: Summary of goodness-of-fit data for selpercatinib, lenvatinib and BSC OS in *RET* fusion-positive TC

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
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]
Generalised gamma	[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]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential	[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; NA: not applicable; OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.

Figure 45: Extrapolations of OS – Selpercatinib, RET fusion-positive TC

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

Table 74: Median and landmark rate estimates of OS for selpercatinib in *RET* fusion-positive TC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	NA	35–50	5–15
Median and landmark survival for each extrapolation				
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: OS: overall survival; *RET*: rearranged during transfection; TC: thyroid cancer.

Figure 46: Extrapolations of OS – Lenvatinib, *RET* fusion-positive TC

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

Table 75: Median and landmark rate estimates of OS for lenvatinib in *RET* fusion-positive TC

Parametric Curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	20–30	5–10	0–2
Median and landmark survival for each extrapolation				
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: OS: overall survival; *RET*: rearranged during transfection; TC: thyroid cancer.

Figure 47: Extrapolations of OS – BSC, *RET* fusion-positive TC

Abbreviations: BSC: best supportive care; OS: overall survival; Prop: proportion; *RET*: rearranged during transfection; TC: thyroid cancer.

Table 76: Median and landmark rate estimates of OS for BSC in RET fusion-positive TC

Parametric Curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	5	0–2	0
Median and landmark survival for each extrapolation				
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic	[redacted]	[redacted]	[redacted]	[redacted]

Spline knot 3	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 2	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 1	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]

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

Based on AIC/BIC criteria, no models demonstrate a substantially superior statistical fit to the observed KM data. As outlined previously, to support this appraisal, UK clinical experts provided estimates of the proportion of patients anticipated to be alive following treatment with each treatment at landmark timepoints. Based on these estimates, the piecewise exponential extrapolation was selected to model OS for selpercatinib, lenvatinib and BSC. This also aligns with the preferences of the Committee in a previous appraisal of selpercatinib in advanced RET-altered TC and MTC (TA742), which was based on an earlier data cut of the same analysis sets of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal, as well as TA535.[2, 25]

As outlined previously, the same extrapolation was selected for each treatment arm, in line with guidance from NICE DSU.

The Weibull extrapolation was explored in a scenario analysis.

B.3.3.5 Time to treatment discontinuation

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.[73]

In addition, during interviews conducted to support this appraisal, UK clinical experts stated that patients may remain on current treatments for a period of time beyond progression due to a lack of subsequent treatments routinely available in UK clinical practice, and symptomatic benefits derived from treatments. As such, in the base case for both the *RET*-mutant MTC and *RET* fusion-positive TC populations, it is assumed that TTD for selpercatinib is equivalent to PFS, with the addition of the mean time from progression to treatment discontinuation as observed in the systemic therapy-naïve populations of the LIBRETTO-001 trial ([redacted] weeks for *RET*-mutant MTC and [redacted] weeks for RET fusion-positive TC). This approach is aligned with the EAG's preferred approach in TA742.[2] For the comparator treatments, TTD is assumed equal to PFS due to a lack of data on TTD; this likely represents a conservative assumption that underestimates the comparator treatment costs.

After discontinuation, all patients are assumed to not receive any subsequent treatments, based on feedback from UK clinical experts collected as part of this appraisal that no subsequent treatments are routinely available in UK clinical practice for patients with advanced, *RET*-altered TC or MTC who experience disease progression on currently available treatments or selpercatinib.[3]

B.3.3.6 Summary of survival approaches

An overview of the approaches adopted to model OS, PFS and TTD for each treatment arm in the base case cost-effectiveness analyses are presented in Table 77 and Table 78 for the RET-mutant MTC and RET fusion-positive TC populations, respectively.

Table 77: Summary of selected base case survival approaches – RET-mutant MTC

Endpoint	Selpercatinib	Cabozantinib	BSC
PFS	Loglogistic		
OS	Stratified Weibull	NA[a]	Stratified Weibull
TTD	Equal to PFS with a delay of [redacted] weeks	Equal to PFS	

[a] OS for cabozantinib is modelled by applying the HR for cabozantinib versus placebo in the *RET*-mutation population to the BSC extrapolation.
Abbreviations: BSC: best supportive care; HR: hazard ratio; NA: not applicable; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 78: Summary of selected base case survival approaches – RET fusion-positive TC

Endpoint	Selpercatinib	Lenvatinib	BSC
PFS	Stratified Weibull		
OS	Piecewise exponential		
TTD	Equal to PFS with a delay of [redacted] weeks	Equal to PFS	

Abbreviations: BSC: best supportive care; HR: hazard ratio; NA: not applicable; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

B.3.3.7 Adverse events

Grade ≥3 adverse events with at least 2% difference in frequency between interventions were included in the model. This approach is consistent with the Assessment Group models in TA516 and TA535.[24, 25] The AEs included for each treatment arm for the *RET*-mutant MTC and *RET* fusion-positive TC populations are presented in Table 79 and Table 80, respectively.

For *RET*-mutant MTC, probabilities of individual AEs for selpercatinib were based on the MTC safety analysis set of the LIBRETTO-001 trial (n=324). Probabilities of individual AEs for cabozantinib and BSC in *RET*-mutant MTC were taken from the EXAM trial.[54, 88]

For *RET* fusion-positive TC, probabilities of individual AEs for selpercatinib were based on the TC safety analysis set of the LIBRETTO-001 trial (n=66). Probabilities of individual AEs for lenvatinib and BSC in *RET* fusion-positive TC were taken from SELECT.[89]

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

Adverse event	Selpercatinib (n=324)	Cabozantinib (n=214)	BSC (n=109)
Diarrhoea	6.79%	21.50%	1.83%
Hand foot syndrome	[redacted]	12.62%	0.00%
Hypertension	21.6%	8.88%	0.00%
ECG QT prolonged	[redacted]	0.00%	0.00%
Decreased weight	[redacted]	9.81%	0.00%
Abdominal pain	3.09%	3.27%	0.92%
Haemorrhage	[redacted]	3.27%	0.92%
Dysphagia	[redacted]	4.21%	0.92%
Fatigue	3.70%	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	2.47%	2.34%	0.92%
Dyspnoea	[redacted]	2.34%	0.00%
Headache	2.78%	0.47%	10.09%
Back pain	[redacted]	4.21%	0.92%
Alanine aminotransferase increased	8.95%	5.14%	1.83%
Aspartate aminotransferase increased	7.72%	1.87%	0.00%
Hyponatraemia	[redacted]	0.93%	0.00%
Lymphopenia	[redacted]	7.48%	10.09%
Pneumonia	[redacted]	0.00%	0.00%
Hypocalcaemia	5.25%	10.75%	0.00%
Dehydration	[redacted]	0.00%	0.00%
Weight increased	[redacted]	0.00%	0.00%
Ascites	[redacted]	0.00%	0.00%
Sepsis	[redacted]	0.00%	0.00%
Hyperkalaemia	[redacted]	0.00%	0.00%
Hypophosphatemia	[redacted]	0.00%	0.00%
Hyperglycaemia	[redacted]	0.00%	0.00%
Hypercalcemia	[redacted]	0.00%	0.00%
Source	LIBRETTO-001, MTC safety analysis set of the (n=324)	EXAM[54, 88]	

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

Table 80: Incidence of Grade 3 or 4 adverse events included in the model for the RET fusion-positive TC population

Adverse event	Selpercatinib (n=66)	Lenvatinib (n=261)	BSC (n=131)
Diarrhoea	7.6%	8.43%	0.00%
Hand foot syndrome	0.0%	3.45%	0.00%
Hypertension	15.2%	42.91%	3.82%
ECG QT prolonged	[redacted]	0.00%	0.00%
Decreased weight	[redacted]	11.88%	0.76%
Fatigue	1.5%	4.60%	1.53%
Decreased appetite	1.5%	5.75%	0.76%
Rash	0.0%	0.00%	0.00%
Asthenia	[redacted]	5.75%	2.29%
Dyspnoea	[redacted]	1.53%	3.05%
Headache	[redacted]	3.07%	0.76%
Back pain	3.0%	0.97%	0.00%
Alanine aminotransferase increased	[redacted]	0.00%	0.00%
Aspartate aminotransferase increased	[redacted]	0.00%	0.00%
Thrombocytopenia	[redacted]	0.00%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%
Pneumonia	[redacted]	0.00%	0.00%
Hypocalcaemia	[redacted]	0.00%	0.00%
Leukopenia	[redacted]	0.00%	0.00%
Nausea	0.0%	2.30%	0.76%
Stomatitis	[redacted]	4.21%	0.00%
Proteinuria	[redacted]	9.96%	0.00%
Neutropenia	[redacted]	0.00%	0.00%
Confused state	[redacted]	0.00%	0.00%
Source	LIBRETTO-001, TC safety analysis set (n=66)	SELECT[25]	SELECT[25]

Abbreviations: BSC: best supportive care; ECG: electrocardiogram; RET: rearranged during transfection; TC: 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 data were collected in LIBRETTO-001 for patients 18 years or older with *RET*-mutant MTC and *RET* fusion-positive TC (Section B.2.6). The questionnaires were answered 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

In the previous appraisal, NICE TA742,[2] the EAG requested that Lilly map the HRQoL data from the LIBRETTO-001 study to the EQ-5D. It was acknowledged by Lilly and the EAG that the resulting EQ-5D-3L estimates were highly implausible, with mean utilities > [redacted] for pre- and post-progression in all subgroups tested. As such, the NICE Committee ultimately elected for the use of utility values that were the same as those used in TA516,[24] and TA535,[25] sourced from a vignette study conducted by Fordham et al (2015).[93]

For completeness, the updated EORTC-QLQ-C30 data from the January 2023 DCO of LIBRETTO-001 were used to estimate utilities based on the EORTC-8D valuation, and mapping algorithms reported by Young *et al.* (2015), Kontodimopoulos *et al.* (2009) and Marriott *et al.* (2017).[104-106] The results are presented in Table 81.

In the MTC population, the mapped utility estimates are highly implausible, with the mean utility for patients with progressed disease higher in all cases, compared to those with progression-free disease. In the TC population, the mapped utility estimates are potentially plausible, although the mean progressed disease utilities are associated with substantial uncertainty (based on HRQoL data from just for patients and 6 assessments overall), while the similarity between the progression-free and progressed disease utilities does not appear to reflect the anticipated loss in HRQoL associated with disease progression.

Table 81: Mapping of EORTC-QLQ-C30 data from LIBRETTO-001 to estimate EQ-5D utilities

Source	Progression-free	Progressed
LIBRETTO-001 EORTC data for *RET*-mutant MTC[b]		
EORTC-8D	[redacted]	[redacted]
Mapped to EQ-5D (Young 2015)[d]	[redacted]	[redacted]
Mapped to EQ-5D (Kontodimopoulos, 2009)	[redacted]	[redacted]
Mapped to EQ-5D (Marriott, 2017)	[redacted]	[redacted]
LIBRETTO-001 EORTC data for *RET* fusion-positive TC		
EORTC-8D	[redacted]	[redacted]
Mapped to EQ-5D (Young 2015)[d]	[redacted]	[redacted]
Mapped to EQ-5D (Kontodimopoulos, 2009)	[redacted]	[redacted]
Mapped to EQ-5D (Marriott, 2017)	[redacted]	[redacted]

[a] Utility estimates also were reported for response and selected adverse events. [b] RET-mutant MTC (any-line population). [c] All post-baseline pre-progression assessments. d Using response mapping.
Abbreviations: CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MTC: medullary thyroid cancer; N: number of patients; n: number of assessments; NR: not reported; RET: REarranged during Transfection; SD: standard deviation; TC: thyroid cancer.

Source: TA621,[107] Lilly data on file, 2023,[73], Young et al. (2015),[104] Marriott et al. (2017),[106] Kontodimopoulos et al. (2009).[105]

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 in August 2019. 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 TA516, TA535 and TA742, sourced from a vignette study conducted by Fordham *et al.* (2015).[2, 24, 25, 93]

B.3.4.4 Adverse reactions

Disutility values are applied to those experiencing AEs to estimate the reduction in quality of life due to the event given the duration of impact of the event. Utility decrements of AEs are presented in Table 82 and Table 83. All adverse reactions are assumed to occur in the first cycle of the model. In line with the model developed by the assessment group in TA516,[24] TA535,[25] and TA742,[2] all AEs were assumed to have a duration of one month (30.44 days).

Table 82: Utility decrements for Grade 3 or 4 adverse events included in the model for the RET-mutant MTC population

Adverse event	Utility decrement	Duration (days)	Sources
Diarrhoea	−0.110	30.4	In NICE TA516 (Assessment Group model), the same utility decrement was assumed for all AEs based on Beusterien et al. (2009), and AEs were assumed to have a duration of 1 month. [108]
Hand foot syndrome	−0.110	30.4	
Hypertension	−0.110	30.4	
ECG QT prolonged	−0.110	30.4	
Decreased weight	−0.110	30.4	
Abdominal pain	−0.110	30.4	
Haemorrhage	−0.110	30.4	
Dysphagia	−0.110	30.4	
Fatigue	−0.110	30.4	
Decreased appetite	−0.110	30.4	
Rash	−0.110	30.4	
Asthenia	−0.110	30.4	
Mucosal inflammation	−0.110	30.4	
Vomiting	−0.110	30.4	
Dyspnoea	−0.110	30.4	
Headache	−0.110	30.4	
Back pain	−0.110	30.4	
Alanine aminotransferase increased	−0.110	30.4	
Aspartate aminotransferase increased	−0.110	30.4	
Hyponatraemia	−0.110	30.4	

Lymphopenia	−0.110	30.4	
Pneumonia	−0.110	30.4	
Hypocalcaemia	−0.110	30.4	
Dehydration	−0.110	30.4	
Weight increased	−0.110	30.4	
Ascites	−0.110	30.4	
Sepsis	−0.110	30.4	
Hyperkalaemia	−0.110	30.4	
Hypophosphatemia	−0.110	30.4	
Hyperglycaemia	−0.110	30.4	
Hypercalcemia	−0.110	30.4	

Abbreviations: ECG: electrocardiogram; MTC: medullary thyroid cancer; RET: rearranged during transfection.
Source: NICE TA516[24]

Table 83 Utility decrements for Grade 3 or 4 adverse events included in the model for the RET fusion-positive TC population

Adverse event	Utility decrement	Source	Duration (days)	Source
Diarrhoea	−0.380	NICE TA535	30.4	NICE TA535
Hand foot syndrome	−0.280	NICE TA535	30.4	NICE TA535
Hypertension	−0.110	NICE TA516	30.4	NICE TA535
ECG QT prolonged	−0.110	NICE TA516	30.4	NICE TA535
Decreased weight	−0.110	NICE TA516	30.4	NICE TA535
Fatigue	−0.080	NICE TA535	30.4	NICE TA535
Decreased appetite	−0.110	NICE TA516	30.4	NICE TA535
Rash	−0.110	NICE TA516	30.4	NICE TA535
Asthenia	−0.110	NICE TA516	30.4	NICE TA535
Dyspnoea	−0.110	NICE TA516	30.4	NICE TA535
Headache	−0.110	NICE TA516	30.4	NICE TA535
Back pain	−0.110	NICE TA516	30.4	NICE TA535
Alanine aminotransferase increased	−0.110	NICE TA516	30.4	NICE TA535
Aspartate aminotransferase increased	−0.110	NICE TA516	30.4	NICE TA535
Thrombocytopenia	−0.110	NICE TA516	30.4	NICE TA535
Lymphopenia	−0.110	NICE TA516	30.4	NICE TA535
Pneumonia	−0.110	NICE TA516	30.4	NICE TA535
Hypocalcaemia	−0.110	NICE TA516	30.4	NICE TA535
Leukopenia	−0.110	NICE TA516	30.4	NICE TA535
Nausea	−0.110	NICE TA516	30.4	NICE TA535
Stomatitis	−0.110	NICE TA516	30.4	NICE TA535
Proteinuria	−0.110	NICE TA516	30.4	NICE TA535
Neutropenia	−0.110	NICE TA516	30.4	NICE TA535

Confused state	−0.110	NICE TA516	30.4	NICE TA535

Abbreviations: ECG: electrocardiogram; RET: rearranged during transfection; TC: thyroid cancer.
Source: : NICE TA516[24]; NICE TA535[25]

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. However, as part of TA742, it was concluded that the utility estimates derived from mapping the EORTC data in LIBRETTO-001 were implausible. As detailed in Section B.3.4.2, the utility estimates based on mapping the updated EORTC data from LIBRETTO-001 continued to be implausible for both the MTC and TC populations, and as such, these were not considered suitable for use in the economic analysis.

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),[93] which were accepted by the NICE Committee in TA516,[24] TA535,[25] and TA742[2] were used in base case analysis of the model and are presented in Table 84. These estimates relate to DTC and were estimated by valuation of health-state descriptions (vignettes).

In the absence of data for patients with TC (other than DTC) or MTC, the health state utility values reported by Fordham et al. (2015),[93] are assumed to be the same across both the MTC and TC populations. As part of TA742, 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]

Table 84: Health-state utility estimates in DTC by Fordham et al. (2015)[93]

Parameter	Mean (SD)
Progression-free	0.80 (0.018)
Progressed	0.50 (0.028)

Abbreviations: DTC: differentiated thyroid cancer; SD: standard deviation.
Note: Utility estimates also were reported for response and selected adverse events.

Age-adjustment

With increasing age, utility is expected to decline. Given the base case time horizon of the model is a lifetime horizon, the model base case includes an annual adjustment factor for age via a multiplicative approach derived from Ara and Brazier *et al.* (2010).[109]

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. Searches were performed on the 12th of August 2019. Details of the SLR search strategy and study selection can be found in Appendix H.

Unit costs were taken from recognised sources for the UK, and costs were also supplemented by clinical opinion sought to support NICE TA742.[2] Relevant resource use and costs were extracted from TA516[24] for the *RET*-mutant MTC populations and from TA535 for the *RET*-fusion TC population, identified from the TLR for past NICE TAs for patients with TC and MTC, and supplemented by clinical opinion gathered to support NICE TA742.[2, 25]

Costs categories included in the model

The analysis was conducted from the NHS and PSS perspective. Appropriate sources of unit costs, such as NHS Reference Costs (2021/22) 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

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Table 85 presents the drug acquisition costs for selpercatinib, cabozantinib and lenvatinib based on their current list prices and licensed doses.

The economic model also accounts for patients that require dose modifications. Table 86 presents the relative dose intensity for selpercatinib and lenvatinib.

The proportion of selpercatinib administrations at each dose level was based on the recorded doses received in the LIBRETTO-001 trial (Table 87), adjusted to reflect the available tablet sizes (40 mg and 80 mg). In the first treatment cycle (model cycles 0–3), no dose reductions are applied. In subsequent treatment cycles, to account for selpercatinib dose reductions, a proportion of patients were assumed to receive a dose level of 20–120mg orally, twice daily, such that the mean dose intensity matched that observed in the LIBRETTO-001 trial ([redacted]% for *RET*-mutant MTC; [redacted]% for *RET* fusion-positive TC). The proportion of patients receiving each dose of selpercatinib in the model are provided in Table 87.

In the absence of dose intensity data for cabozantinib, the selpercatinib dose intensity observed for patients with *RET*-mutant MTC in the LIBRETTO-001 trial was also applied to cabozantinib. For lenvatinib, dose intensity was informed by the relative dose intensity for each treatment reported in NICE TA535.[25]

The total costs for each treatment are derived by applying the drug acquisition costs to the modelled TTD, as described in Section B.3.3.5. No drug wastage is assumed in the base case cost-effectiveness analysis. However, a scenario analysis is conducted where drug wastage is assumed, in which minimum cost of whole tablet combinations is used to provide the require dose for each four-week prescription.

Table 85: Drug acquisition costs for selpercatinib, cabozantinib and lenvatinib

Regimen	Regimen description	Capsule strength	Capsules per pack	Pack cost	PAS discount	PAS pack cost
Selpercatinib	160 mg, orally, twice daily	80 mg	112	£8,736.00	[redacted]	[redacted]
		40 mg	168	£6,552.00		[redacted]
Cabozantinib	140 mg, orally, once daily	80 mg	112	£4,800.00	NA	NA
		20 mg	112	£4,800.00	NA	NA
Lenvatinib	24mg, orally, once daily	4 mg	30	£1,437.00	NA	NA
		10 mg	30		NA	NA

One pack size is presented for each drug in the table above; however, the model background calculations use all available vial sizes in the drug wastage calculation.
Abbreviations: BNF: British National Formulary; PAS: Patient Access Scheme.
Source: List prices for each treatment are sourced from the BNF.[110-114]

Table 86: Relative dose intensity for selpercatinib and comparators

Regimen	*RET*-mutant MTC	*RET* fusion-positive TC	Source
Selpercatinib[a] (used for comparators where no data are available)	[redacted]	[redacted]	Lilly data on file, LIBRETTO-001
Cabozantinib	[redacted]	NA	Assumed same as selpercatinib, based on LIBRETTO-001
Lenvatinib	NA	71.67%	NICE TA535

[a]These data are not used for selpercatinib in the model. The proportion of patients receiving each selpercatinib dose was based on the recorded doses received in the LIBRETTO-001 trial, adjusted to reflect the available tablet sizes (40 mg and 80 mg).
Abbreviations: MTC: medullary thyroid cancer; NICE: National Institute for Health and Care Excellence; RET: rearranged during transfection; TC: thyroid cancer.
Source: Lilly data on file[73]; NICE TA535[25]

Table 87: Doses of selpercatinib received by RET-mutant MTC and RET-fusion-positive TC patients in the economic model

Dose (mg)	*RET*-mutant MTC Proportion of patients on dose (%)	*RET* fusion-positive TC Proportion of patients on dose (%)
Treatment cycle 1		
160	[redacted]	[redacted]
120	[redacted]	[redacted]
80	[redacted]	[redacted]
Treatment cycle 2		
160	[redacted]	[redacted]
120	[redacted]	[redacted]
80	[redacted]	[redacted]
60	[redacted]	[redacted]
40	[redacted]	[redacted]
20	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; NA: not applicable; TC: thyroid cancer.

Drug administration and monitoring

Administration costs were based on NHS Reference Costs (2021/22). For selpercatinib and other oral drugs, 12 minutes of pharmacy time (£11.40) was assumed every 30 days.[115] This is aligned with the approach accepted as part of TA742.

In addition, the costs of 7 ECGs were applied as part of the monitoring costs for selpercatinib, in line with the requirements for the SmPC for selpercatinib.[1] The cost of each ECG (£159.36) was based on NHS reference costs (2021/22; EY51Z).

Best supportive care

Best supportive care was assumed to be monitoring and palliative care, as included in the health-state costs in Section B.3.5.2.

B.3.5.2 Health-state unit costs and resource use

The types of resource and frequency of use in Year 1 and each subsequent year in the PF and PD health states in the MTC and TC analyses were based on the TA516 Assessment Group model (consistent with NICE TA742), which in turn were based on previously obtained clinical expert opinion.[2, 24] The costs and resource use frequency assumed in the base case are presented in Table 88.

Resource use for the *RET*-mutant MTC and *RET* fusion-positive TC populations is assumed to be the same in the base case. For BSC, the resource use of the progression-free health state was assumed to be the same as for the progressed health state, as recommended by the NICE EAG in TA742.[2]

Table 88: Unit costs and resource use per year in RET-mutation MTC and RET-fusion positive TC

Resource	PF	PD	Unit cost	Unit cost source
Consultant-led outpatient visits (range)	12 (4–16)	6 (4–12)	£162.93	NHS Reference Costs (2021/22) consultant-led, non-admitted face-to-face attendance, follow-up WF01A
Nurse-led outpatient visits (range)	4 (0–6)	6 (0–6)	£130.74	NHS Reference Costs (2021/22) non-consultant-led, non-admitted face-to-face attendance, follow-up WF01A
Blood tests	12	6	£4.70	NHS Reference Costs (2021/22) directly accessed pathology, phlebotomy DAPS08
CT scan	4	4	£99.88	NHS Reference Costs (2021/22) outpatient, computerized tomography scan of more than 3 areas RD27Z

For BSC, the resource use of the progression-free health state was assumed to be the same as for the progressed health state, as recommended by the NICE EAG in TA742.
Abbreviations: CT: computerised tomography; ECG: electrocardiogram; MTC: medullary thyroid cancer; PF: progression-free; PD: progressed disease; RET: rearranged during transfection; TC: thyroid cancer.
Source: NICE TA516[24]

End-of-life palliative care

The costs associated with palliative care and palliative chemotherapy is applied at the point of death to all patients (Table 89). These costs are based on the data used in the Assessment Group and Sanofi model in TA516[24] which were, in turn, derived from the NHS Reference Costs and the Personal Social Services Research Unit (PSSRU),[24] which is consistent with NICE TA742.[2]

Table 89: Cost of end-of-life palliative care in MTC and TC

Resource	Cost	Assumptions
Palliative care	£10,676.25	NICE TA516, PSSRU 2022
Palliative chemotherapy	£1,016.14	NHS Reference Costs (2021/22), other, procure chemotherapy drugs for regimens in band 1-10, SB01Z-SB10Z

Abbreviations: MTC: medullary thyroid cancer; PSSRU: Personal Social Services Research Unit; TC: thyroid cancer.
Source: NICE TA516[24]

Subsequent treatments

Following disease progression, patients in all treatment arms are assumed to receive no active subsequent treatments. This is based on feedback from UK clinical experts who stated that no subsequent treatments are available routinely in UK clinical practice for patients with RET-altered TC or MTC following disease progression after their first systemic therapy; although selpercatinib is available via the CDF, this is not considered a routinely available treatment for the purposes of this appraisal. This assumption is aligned with the Assessment Group's model in TA516 and TA535.[24, 25]

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs for adverse events are presented in Table 90 and Table 91. Costs were taken from NHS Reference Costs (2021/22; where available), based on the cost codes used as part of TA516 and TA742.[2, 24]

Table 90: Adverse event unit costs for the RET-mutant MTC population

Adverse event	Mean cost per episode (£)	Source
Diarrhoea	3,407.28	NHS Reference costs 2021/22; TA516 (FD10H-M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, with CC Score 9+; Non-Elective inpatient)
Hand foot syndrome	1,646.87	NHS Reference costs 2021/22; TA516 (JD07K Skin Disorders without Interventions, with CC Score 0-1; Non-Elective Inpatient)
Hypertension	2,300.49	NHS Reference costs 2021/22; TA516 (EB04Z Hypertension; Non-Elective Inpatient)
ECG QT prolonged	1,649.11	NHS Reference costs 2021/22; TA516 (EB07E Arrhythmia or Conduction Disorders, with CC Score 0–3; Non-Elective Inpatient)
Decreased weight	3,042.95	NHS Reference costs 2021/22; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Abdominal pain	1,789.01	NHS Reference costs 2021/22; TA516 (FD05B Abdominal Pain without Interventions; Non-Elective Inpatient)
Haemorrhage	500.00	Assumption
Dysphagia	1,367.91	NHS Reference costs 2021/22; TA516 (CB02F Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0; Non-Elective Inpatient)
Fatigue	0.00	Assumption
Decreased appetite	3,042.95	NHS Reference costs 2021/22; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Rash	1,646.87	NHS Reference costs 2021/22; TA516 (JD07K Skin Disorders without Interventions, with CC Score 0-1; Non-Elective Inpatient)

Asthenia	0.00	Assumption
Mucosal inflammation	1,949.19	NHS Reference costs 2021/22; TA516 (FD01J Gastrointestinal Infections without Interventions, with CC Score 0-1; Non-Elective Inpatient)
Vomiting	3,042.95	NHS Reference costs 2021/22; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Dyspnoea	1,446.19	NHS Reference costs 2021/22; TA516 (DZ19N Other Respiratory Disorders without Interventions, with CC Score 0-4; Non-Elective Inpatient)
Headache	0.00	Assumption
Back pain	2,096.09	NHS Reference costs 2021/22; TA516 (HC32K Low Back Pain without Interventions, with CC Score 0-2; Non-Elective Inpatient)
Alanine aminotransferase increased	0.0	Assumption
Aspartate aminotransferase increased	0.00	Assumption
Hyponatremia	1,708.97	Assumption
Lymphopenia	4,776.75	NHS Reference costs 2021/22; Assumption (SA17H Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 0-2; Non-Elective Inpatient)
Pneumonia	2,067.76	NHS Reference costs 2021/22; TA516 (DZ11V Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3; Non-Elective Inpatient)
Hypocalcaemia	1,708.97	NHS Reference costs 2021/22; Assumption (SA09L Other Red Blood Cell Disorders with CC Score 0-1; Non-Elective Inpatient)
Dehydration	500.00	Assumption
Weight increased	0.00	Assumption
Ascites	1,789.01	NHS Reference Costs (2021/22)
Sepsis	5,779.96	NHS Reference costs 2021/22 (WJ06D-F Sepsis with Single Intervention, with CC Score 0-9+; Non-Elective inpatient)
Hyperkalaemia	0.00	Assumption
Hypophosphatemia	0.00	Assumption
Hyperglycaemia	0.00	Assumption
Hypercalcemia	0.00	Assumption

Abbreviations: ECG: electrocardiogram.
Source: NICE TA516[24]

Table 91: Adverse event unit costs for the RET fusion-positive TC population

Adverse event	Mean cost per episode (£)	Source
Diarrhoea	3,407.28	NHS Reference costs 2021/22; TA516 (FD10H-M Non-Malignant Gastrointestinal Tract Disorders

		with/without (single/multiple) Interventions, with CC Score 9+; Non-Elective inpatient)
Hand foot syndrome	1,646.87	NHS Reference costs 2021/22; TA516 (JD07K Skin Disorders without Interventions, with CC Score 0-1; Non-Elective Inpatient)
Hypertension	2,300.49	NHS Reference costs 2021/22; TA516 (EB04Z Hypertension; Non-Elective Inpatient)
ECG QT prolonged	1,649.11	NHS Reference costs 2021/22; TA516 (EB07E Arrhythmia or Conduction Disorders, with CC Score 0–3; Non-Elective Inpatient)
Decreased weight	3,042.95	NHS Reference costs 2021/22; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Fatigue	0.00	Assumption
Decreased appetite	3,042.95	NHS Reference costs 2021/22; Assumption (FD04E Nutritional Disorders without Interventions, with CC Score 0-1, Non-Elective Inpatient)
Rash	1,646.87	NHS Reference costs 2021/22; TA516 (JD07K Skin Disorders without Interventions, with CC Score 0-1; Non-Elective Inpatient)
Asthenia	0.00	Assumption
Dyspnoea	1,446.19	NHS Reference costs 2021/22; TA516 (DZ19N Other Respiratory Disorders without Interventions, with CC Score 0-4; Non-Elective Inpatient)
Headache	0.00	Assumption
Alanine aminotransferase increased	0.00	Assumption
Aspartate aminotransferase increased	0.00	Assumption
Thrombocytopenia	0.00	Assumption
Lymphopenia	4776.75	NHS Reference costs 2021/22; Assumption (SA17H Malignant Disorders of Lymphatic or Haematological Systems, with CC Score 0-2; Non-Elective Inpatient)
Pneumonia	2,067.76	NHS Reference costs 2021/22; TA516 (DZ11V Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3; Non-Elective Inpatient)
Hypocalcaemia	1,708.97	NHS Reference costs 2021/22; Assumption (SA09L Other Red Blood Cell Disorders with CC Score 0-1; Non-Elective Inpatient)
Leukopenia	0.00	Assumption
Nausea	0.00	Assumption
Stomatitis	0.00	Assumption
Proteinuria	0.00	Assumption
Neutropenia	0.00	Assumption
Confused state	0.00	Assumption

Abbreviations: ECG: electrocardiogram.
Source: NICE TA516[24]

B.3.5.4 Miscellaneous unit costs and resource use

RET next generation sequencing (NGS) and fluorescent in situ hybridisation (FISH) testing are included in the 2023/2024 National Genomic Test Directory for Cancer, with NGS panel testing now available on the NHS for all solid and blood cancers. In England, this transition to NGS testing means that *RET* rearrangements are routinely tested alongside other oncogenic drivers in a standardised manner across different centres.[7, 8] Thus it is not anticipated that approval of selpercatinib would result in any additional costs to the healthcare system, specifically related to testing for *RET* alterations (consistent with NICE TA742).[2]

However, in line with the Committee preferences in the evaluation of selpercatinib as a treatment for RET fusion-positive NSCLC (TA911), the cost of RET testing has been included in the base case cost-effectiveness analysis to reflect any costs associated with RET testing. Estimates of the screen-positive rate in each population and the cost of the test are presented in Table 92.

Table 92: Diagnostic testing inputs for scenario analysis

Parameter	*RET*-mutant MTC	*RET* fusion-positive TC
Screen-positive rate	61.2%[a] Source: Derived from Taccaliti et al. (2011)[116] and Wells et al. (2015)[117]	6.8% Source: Liu et al., 2014[118]
RET test cost	£34 Source: TA911[119]	

[a] Wells et al. (2015)[117] reported that 50% of sporadic MTCs and 95% of hereditary MTCs have *RET* mutations. Taccaliti et al. (2011)[116] reported that 75% of MTC cases are sporadic and 25% are hereditary. 0.5 × 0.75 + 0.95 × 0.25 = 0.612.
Abbreviations: FISH: fluorescence in situ hybridization; MTC: medullary thyroid cancer; NGS: next generation sequencing; NSCLC: non–small cell lung cancer; TC: thyroid cancer.

B.3.6 *Severity*

The severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR) and Lumanity was used to calculate the absolute and proportional severity modifiers.[120] A summary of the features of the QALY shortfall analysis is provided in Table 93. In line with the NICE reference case, the Hernandez-Alava 2017 study, which mapped the EQ-5D-5L to the 3L, was used (Table 94).[121, 122]

The results demonstrate that for the *RET*-mutant MTC population, selpercatinib is eligible for a 1.2x severity modifier when compared to both cabozantinib and BSC. In the *RET*-fusion positive TC population, selpercatinib is eligible for a 1.2x severity modifier when compared with BSC but is not eligible for a severity modifier versus lenvatinib (Table 94). These results were also consistent across all scenario analyses.

Table 93: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
***RET*-mutant MTC**		

Sex distribution	39.0%	Section B.3.3.1, Table 59
Starting age (mean)	[redacted]	Section B.3.3.1, Table 59
Health state utility: PF	0.80	Section B.3.4.5, Table 84
Health state utility: PD	0.50	Section B.3.4.5, Table 84
***RET*-fusion Positive TC**		
Sex distribution	50.8%	Section B.3.3.1, Table 59
Starting age	[redacted]	Section B.3.3.1, Table 59
Health state utility: PF	0.80	Section B.3.4.5, Table 84
Health state utility: PD	0.50	Section B.3.4.5, Table 84

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

Table 94: Summary of QALY shortfall analysis

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
***RET*-mutant MTC**				
[redacted]	Cabozantinib: 2.11	[redacted]	[redacted]	1.2
[redacted]	BSC: 1.51	[redacted]	[redacted]	1.2
***RET*-fusion positive TC**				
[redacted]	Lenvatinib: 2.62	[redacted]	[redacted]	1
[redacted]	BSC: 1.27	[redacted]	[redacted]	1.2

Abbreviations: EQ-5D-3/5L: Euro-QoL Questionnaire 5 Dimensions 3/5 levels; HSE: Health Survey for England; MVH: Measurement and Valuation of Health study; QALY: quality-adjusted life year.

B.3.7 *Uncertainty*

Due to the rarity of advanced *RET* fusion-positive TC, data from comparator studies that did not specifically recruit patients with *RET* alterations had to be used to inform the ITCs which generate comparative efficacy estimates for selpercatinib versus relevant comparators. Whilst there may be potential for this to result in a degree of uncertainty in the comparative efficacy estimates, as highlighted in Section B.1.3.1, a number of studies have demonstrated that the real prognostic influence of *RET* alterations remains unclear.

As part of this appraisal, UK clinical experts highlighted that patients with *RET*-altered TC and MTC may face a poorer prognosis versus patients with wild-type TC and MTC, indicating that results of the SELECT trial, which did not specifically include or report results for a *RET*-altered patient population, may be overestimating the efficacy of the comparator treatments in some cases, as further outlined in Section B.2.9.3. Nevertheless, this approach is in line with that accepted in previous NICE evaluations of selpercatinib, including TA742.[2]

In addition, efficacy data for the comparators were not available for populations of patients who had not received any previous treatments for advanced disease. As such, it was necessary to use line-agnostic data for both the comparators and selpercatinib; in the ITCs, the efficacy of selpercatinib is informed by the combined efficacy analysis sets for both the MTC and TC populations, which included treatment-naïve and previously treated patients receiving selpercatinib. Although the line-agnostic nature of the ITCs may introduce some uncertainty, the increased sample size of the combined efficacy analysis sets, compared with the treatment-naive analysis sets, results in increased robustness and precision of the comparative efficacy estimates.

Data on TTD were not available for the comparator treatments. As such, for each comparator, TTD was assumed to be equal to PFS. Based on feedback from UK clinical experts that patients remain on treatment following progression due to the lack of routinely available subsequent treatments, it is likely that this assumption underestimates the costs associated with cabozantinib and lenvatinib. As such, although a source of uncertainty, this represents a conservative assumption that is likely to bias against selpercatinib.

The data for OS from LIBRETTO-001 are currently immature, which may lend some uncertainty to the analysis, particularly regarding the long-term extrapolation of these data. However, this was mitigated through extensive consultations with UK-based clinical experts as part of this appraisal regarding the anticipated long-term survival for patients with *RET*-altered MTC and TC treated with selpercatinib. The selection of base case extrapolations was based on a rigorous process, which placed a high degree of emphasis on the feedback from UK clinical experts to ensure that clinically plausible long-term survival estimates are produced by the cost-effectiveness model; the resulting extrapolations are aligned with the committee's preferred extrapolations used for an earlier DCO of the same selpercatinib LIBRETTO-001 datasets as part of TA742, providing further confidence in the modelled survival estimates.

B.3.8 *Managed access proposal*

Lilly consider that the evidence presented in this submission are sufficiently robust for routine commissioning. When compared to the original 16th December 2019 DCO providing the evidence base for reimbursement of selpercatinib as part of TA742[2] via the CDF, the 13th January 2023 DCO provides over two years worth of additional data. In the cabozantinib/vandetanib naïve *RET*-mutant MTC patient population, a median duration of follow-up of [redacted] was observed for OS and higher patient numbers are now available (compared with the previous DCO), with the systemic therapy naïve TC patient population increasing from [redacted] to N=24 patients between the original and final DCOs.

As shown in Appendix N, efficacy trends between the 16th December 2019, 15th June 2021 and 13th January 2023 DCOs have remained consistent over time, demonstrating deep and durable responses in patients anticipated to translate to survival benefits in the long-term. [redacted]

If the Committee deem that a period of Managed Access would be necessary to resolve the uncertainty in this evaluation, potential sources of data would be:

- The LIBRETTO-531 trial: an ongoing, multicentre, randomised, open-label Phase III trial comparing the safety and efficacy of selpercatinib versus the physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor naïve *RET*-mutant MTC.[92] Data will only be provided for the MTC population of relevance to this submission, furthermore, patients are permitted to cross-over from the comparator arm to the selpercatinib arm following disease progression.
- Collection of data via the systemic anticancer therapy (SACT) cohort

B.3.9 *Summary of base-case analysis inputs*

A summary of inputs for the base case analysis is presented in Table 95.

Table 95: Summary of variables applied in the economic model

Variable	*RET*-mutant MTC	*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	[redacted]	[redacted]	Section B.3.3.1
Percent female	39.0%	50.8%	
Clinical inputs			
PFS (selpercatinib)	Log-logistic	Stratified Weibull	Section B.3.2
PFS (comparators)			
OS (selpercatinib)	Stratified Weibull (cabozantinib modelled via HR applied to BSC)	Piecewise exponential	
OS (comparators)			
TTD (selpercatinib and cabozantinib)	Equal to progression plus a delay of [redacted] weeks	Equal to progression plus a delay of [redacted] weeks	Section B.3.3.5
Adverse events, incidence	Table 79	Table 80	Section B.3.3.7
Utility inputs			
Utility for PF, mean (SD)	0.80		Section B.3.4.5
Utility for PD, mean (SD)	0.50		
AE disutilities	Table 82	Table 83	Section B.3.4.4
Cost inputs			
Selpercatinib PAS pack cost (112 x 80 mg capsules)	[redacted]		Section B.3.5.1
Selpercatinib PAS pack cost (168 x 40 mg capsules)	[redacted]		
Cabozantinib acquisition cost (112 caps)	£4,800.00		

Lenvatinib acquisition cost (30 caps)	£1,437.00		
Administration cost per treatment cycle (all treatments)	£11.40		
ECG cost (selpercatinib only)	£159.36		
Mean RDI (selpercatinib and cabozantinib for RET-mutant MTC)	[redacted]		
Mean RDI (selpercatinib for RET-fusion positive TC)	[redacted]		
Mean RDI (lenvatinib)	71.67%		
PF average resource use frequencies	Table 88		Section B.3.5.2
PD average resource use frequencies	Table 88		
Consultant-led outpatient visits unit cost	£162.93		
Nurse-led outpatient visits unit cost	£130.74		
ECG unit cost	£222.62		
Blood tests unit cost	£4.70		
CT scan unit cost	£99.88		
Palliative care cost	£10,676.25		
Palliative chemotherapy cost	£1,016.14		
Cost of RET testing	£34.00		
Adverse events, unit costs	Table 90	Table 91	Section B.3.5.3

Abbreviations: BSC: best supportive care; MTC: medullary thyroid cancer; NA: 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.3.9.1 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 96, 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 Table 103.

Table 96: Modelling assumptions

Parameter	Assumption	Justification	Addressed in scenario analysis
Survival models			
PFS curves	*RET*-mutant MTC: loglogistic (all treatment arms) *RET* fusion-positive TC: stratified Weibull (all treatment arms)	The selection of extrapolation for PFS was based on statistical fit, visual inspection and long-term clinical plausibility, based on feedback from UK clinical experts collected as part of this appraisal. The selected extrapolations were consistent with those preferred by the NICE Committee in TA742.	Scenario analyses have been conducted for both populations in which alternative extrapolations are selected to model PFS (applied to all treatment arms).
OS curves	*RET*-mutant MTC: stratified Weibull (selpercatinib and BSC) *RET* fusion-positive TC: piecewise exponential (all treatment arms)	The selection of extrapolation for OS was based on statistical fit, visual inspection and long-term clinical plausibility, based on feedback from UK clinical experts collected as part of this appraisal. The selected extrapolations were consistent with those preferred by the NICE Committee in TA742.	Scenario analyses have been conducted for both populations in which alternative extrapolations are selected to model OS (applied to all treatment arms).
Modelling of OS for cabozantinib	OS HR for cabozantinib was applied to the OS extrapolation for 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 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 as part of TA742	Scenario analyses have been conducted exploring alternative extrapolations for BSC, which inherently explores alternative long-term survival estimates of OS for cabozantinib.
TTD	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks and [redacted] weeks applied to selpercatinib in the RET-mutant MTC and RET fusion-positive TC populations, respectively.	The delay applied to PFS for selpercatinib is based on the mean time from progression to treatment discontinuation observed in LIBRETTO-001 for the cabozantinib/vandetanib-naïve MTC	A scenario analysis has been conducted in which TTD is assumed equal to PFS for all treatment arms.

	For all comparators, TTD is assumed equal to PFS.	population and the systemic therapy-naive TC population. This approach is aligned with the EAG's preferred approach in TA742 and feedback from UK clinical experts, who indicated that given the lack of subsequent treatment options available to this patient population, patients would likely continue to receive treatment for a short time upon disease progression.[1] For the comparators, in the absence of robust TTD data, TTD is assumed equal to PFS. This represents a conservative assumption as patients are likely to remain on treatment for a period of time following progression, due to a lack of subsequent treatments available routinely in UK clinical practice.	
Costs			
Drug acquisition costs	Costs of drug wastage were not included in the base case analysis.	This is a common approach for oral medications and aligns with expected UK clinical practice.	A scenario analysis was conducted in which costs of drug wastage are included.
	In the 4th treatment cycles and beyond, to account for dose reductions for selpercatinib and all comparators, a proportion of patients were assumed to reduced dose of each treatment, to match the relative dose intensities for each treatment, as outlined in Section B.3.5.1.	This is aligned with the available data from the relevant clinical trials for selpercatinib and comparators and the SmPCs for each treatment.	No scenario analyses have been conducted varying this assumption as it aligns with available data from relevant clinical trials and the SmPCs for each treatment.
Subsequent treatments	Patients in all treatment arms are assumed to receive no active subsequent treatments	This is based on feedback from UK clinical experts who stated that no subsequent treatments are available routinely in UK clinical practice for patients with RET-	No scenario analyses have been conducted varying this assumption as it aligns with anticipated UK clinical

		altered TC or MTC following disease progression after their first systemic therapy, and is aligned with assumptions used in the Assessment Group's model in TA516 and TA535.[24, 25]	practice, based on feedback from UK clinical experts.
RET testing	A cost associated with RET-testing of £34 is included in the base case	As described in Section B.3.5.4, *RET* NGS and FISH testing are included in the 2023/2024 National Genomic Test Directory for Cancer, with NGS panel testing now available on the NHS for all solid and blood cancers. As such, testing for *RET* rearrangements are routinely tested alongside other oncogenic drivers across many centres. However, to reflect any costs associated with testing of *RET* rearrangements and to align with the Committee's preferences in TA911, the cost of *RET*-testing has been included in the base case.	No scenario analyses have been conducted varying this assumption as it represents a conservative assumption and aligns with the Committee's preference in TA911.
Utility values			
Utility values	Utility values sourced reported by Fordham et al. (2015) are used to inform health state utility values for the MTC and TC populations[93]	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 and RET-fusion positive TC. However, the utility estimates based on mapping the EORTC data from LIBRETTO-001 were implausible for both the MTC and TC populations (Section B.3.4.2), and as such, these were not considered suitable for use in the economic analysis. Given no utility estimates specific to patients with RET-mutant MTC or RET	As this assumption has been accepted by the NICE committee in a number of previous appraisals in TC and MTC, including TA742, no scenario analyses varying this assumption have been conducted.[2]

		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 used in the base case. This approach is aligned with that adopted in TA742.[2]	
AEs			
AE proportions	Grade ≥3 adverse events with at least 2% difference in frequency between interventions were included in the model	This is consistent with the approach commonly adopted in oncology economic models and the approach adopted in the Assessment Group models in TA516 and TA535.[24, 25]	No scenario analyses varying this assumption have been conducted.

Abbreviations: AE: adverse event; BSC: best supportive care; EAG: External Assessment Group; EORTC QLQ: European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; MTC: medullary thyroid cancer; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; SLR: systematic literature review; SmPC: Summary of Product Characteristics; TA: Technology Appraisal; TC: thyroid cancer; TTD: time to treatment discontinuation .

B.3.10 *Base-case results*

B.3.10.1 Base-case cost-effectiveness analysis results

Probabilistic base case results

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

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 may be found in the cost-effectiveness model provided alongside this submission. 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

As discussed in Section B.1.3.3, for patients with *RET*-mutant MTC the only treatment that is currently recommended in the UK is cabozantinib.[24] However, due to its poor AE profile, a subset of patients are ineligible for cabozantinib, with BSC representing their only treatment option. 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 the base-case pairwise comparisons for selpercatinib (at PAS price) versus cabozantinib and BSC in *RET*-mutant MTC are presented in Table 97, with net health benefit (NHB) results presented in Table 98 (at selpercatinib PAS price). For reference, results of a fully incremental analysis (at selpercatinib PAS price) are presented in Table 99.

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 £89,639 for patients treated with cabozantinib (an incremental cost of £[redacted]), and £17,022 for patients treated with BSC (an incremental cost of £[redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with 2.11 for patients treated with cabozantinib (an incremental QALY gain of [redacted]) and 1.51 for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of £29,738 and £40,184 per QALY gained versus cabozantinib and BSC, respectively. At a willingness-to-pay threshold (WTP) of £30,000, the NHB for selpercatinib versus cabozantinib is positive ([redacted]) and the NHB for selpercatinib versus BSC is negative ([redacted]), not taking into account the severity modifier. However, as highlighted in Section B.3.6, selpercatinib is eligible for a 1.2x severity modifier when compared with cabozantinib and BSC.

The results presented include the confidential PAS discount provided alongside this submission. It should also be noted that cabozantinib is associated with a simple discount PAS which is not visible to the Company, therefore, cost effectiveness analyses are based upon list prices for all active interventions other than selpercatinib.

Table 97: Pairwise probabilistic base-case results for selpercatinib in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYG[a]	Incremental QALYs[a]	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	89,639	3.412	2.11	[redacted]	[redacted]	[redacted]	29,738
BSC	17,022	2.67	1.51	[redacted]	[redacted]	[redacted]	40,184

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

Table 98: Probabilistic net health benefit for selpercatinib in RET-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	NHB at £20,000[a]	NHB at £30,000[a]
Selpercatinib	[redacted]	[redacted]	-	-	-	-
Cabozantinib	89,639	2.11	[redacted]	[redacted]	[redacted]	[redacted]
BSC	17,022	1.51	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 99: Fully incremental probabilistic base-case results for *RET*-mutant MTC (at selpercatinib PAS price)

	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	17,022	1.51	-	-
Cabozantinib	89,639	2.11	Extendedly dominated	121,028
Selpercatinib	[redacted]	[redacted]	40,184	40,184

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.

RET fusion-positive TC

An overview of the pairwise probabilistic base-case cost-effectiveness results for the RET fusion-positive TC population can be found in Table 100 (at selpercatinib PAS price), with NHB results presented in Table 101. In line with the approach taken for the RET-mutant MTC population, results of a fully incremental cost-effectiveness analysis are presented in Table 102 (at selpercatinib PAS price).

The base case cost-effectiveness results show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be £[redacted] compared with £96,451 for patients treated with lenvatinib (incremental cost of £[redacted]) and £16,006 for patients treated with BSC (incremental costs are £[redacted]).

The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with 2.62 for patients treated with lenvatinib (an incremental QALY gain of [redacted]), resulting in an ICER of £34,620 per QALY gained versus lenvatinib. The total QALYs for patients receiving BSC are estimated to be 1.27 for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER for selpercatinib of £43,067 per QALY gained versus BSC. The NHB at a £30,000 WTP is negative for both lenvatinib and BSC [redacted] and [redacted], respectively). As highlighted in Section B.3.6, selpercatinib is eligible for a 1.2x severity modifier when compared with BSC. This severity modifier is not included in these cost-effectiveness results.

The results presented include the confidential PAS discount provided alongside this submission. It should also be noted that lenvatinib is associated with a simple discount PAS which is not visible to the Company, therefore, cost effectiveness analyses are based upon list prices for all active interventions other than selpercatinib.

Table 100: Pairwise probabilistic base-case results for selpercatinib versus lenvatinib and BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Lenvatinib	96,451	4.122	2.620	[redacted]	[redacted]	[redacted]	34,620
BSC	16,006	2.303	1.272	[redacted]	[redacted]	[redacted]	43,067

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

Table 101: Probabilistic net health benefit for selpercatinib versus lenvatinib and BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	NHB at £20,000[a]	NHB at £30,000[a]
Selpercatinib	[redacted]	[redacted]	-	-	-	-
Lenvatinib	96,451	2.620	[redacted]	[redacted]	[redacted]	[redacted]
BSC	16,006	1.272	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 102: Fully incremental probabilistic base-case results for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	16,006	1.272	-	-
Lenvatinib	96,451	2.620	Extendedly dominated	59,677
Selpercatinib	[redacted]	[redacted]	43,067	43,067

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

B.3.11 *Exploring uncertainty*

B.3.11.1 Probabilistic sensitivity analysis

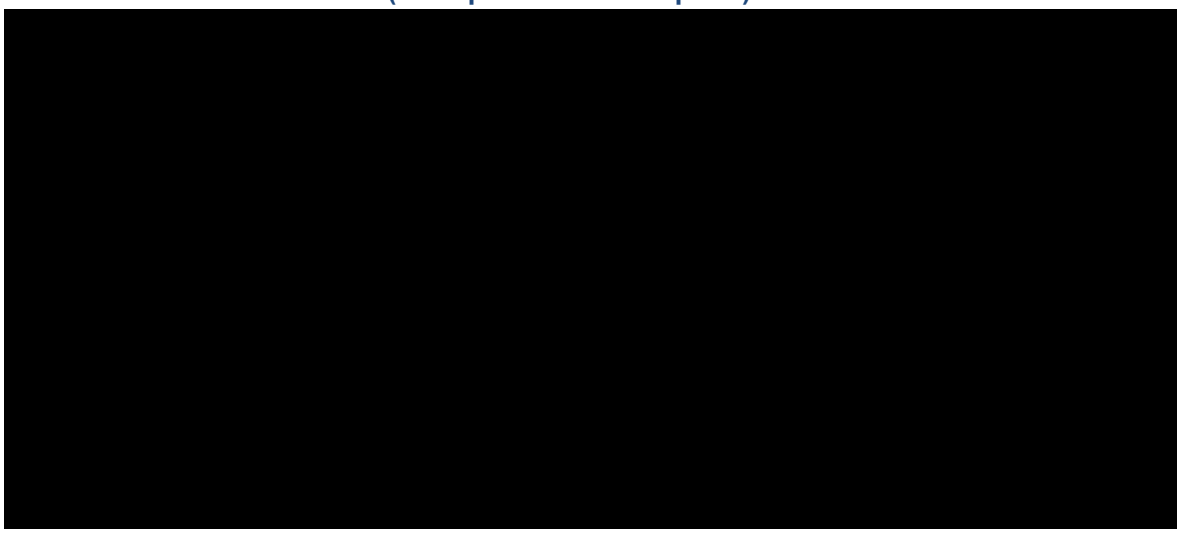
RET-mutant MTC

Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves versus cabozantinib and BSC are presented in Figure 48 and Figure 49.

Figure 48: Cost-effectiveness plane scatterplot for selpercatinib versus cabozantinib and BSC – *RET*-mutant MTC (at selpercatinib PAS price)

Generated using 1,000 iterations of the PSA.
Abbreviations: MTC: medullary thyroid cancer; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

Figure 49: Cost-effectiveness acceptability curves for selpercatinib versus cabozantinib and BSC – *RET*-mutant MTC (at selpercatinib PAS price)



Generated using 1,000 iterations of the PSA.
Abbreviations: MTC: medullary thyroid cancer; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

RET fusion-positive TC

Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves for selpercatinib versus lenvatinib and BSC are presented in Figure 50 and Figure 51.

Figure 50: Cost-effectiveness plane scatterplot for selpercatinib versus lenvatinib and BSC – *RET* fusion-positive TC (at selpercatinib PAS price)

Generated using 1,000 iterations of the PSA.
Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

Figure 51: Cost-effectiveness plane scatterplot for selpercatinib versus lenvatinib and BSC – *RET* fusion-positive TC (at selpercatinib PAS price)

Generated using 1,000 iterations of the PSA.
Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

B.3.11.2 Deterministic sensitivity analysis

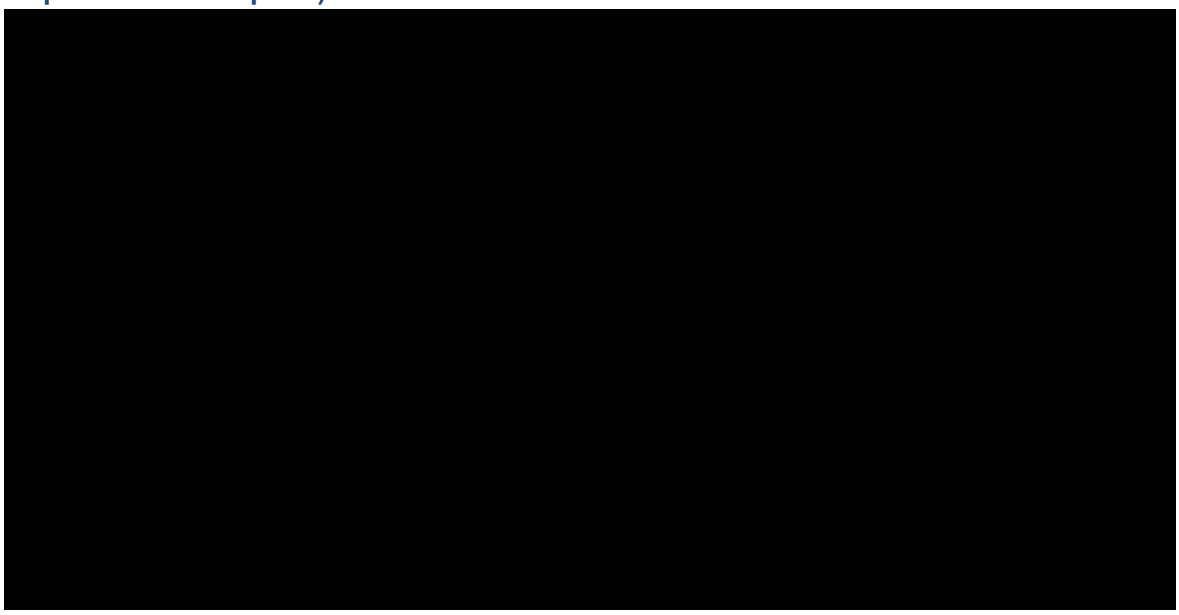
RET-mutant MTC

The 25 most influential variables in the deterministic sensitivity analyses (DSA) for the analysis of selpercatinib versus cabozantinib and selpercatinib versus BSC are presented as tornado plots in Figure 52 and Figure 53, respectively. The most influential parameters were the discount rate for outcomes and costs, the progression-free health state utility value and the progression-free health state costs. For the comparison of selpercatinib versus cabozantinib, the OS for cabozantinib represents another influential parameter.

Figure 52: Tornado plot (ICER) of selpercatinib versus cabozantinib – *RET*-mutant MTC (at selpercatinib PAS price)

Abbreviations: ICER: incremental cost-effectiveness ratio; MTC: medullary thyroid cancer.

Figure 53: Tornado plot (ICER) of selpercatinib versus BSC – RET-mutant MTC (at selpercatinib PAS price)



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 relevant comparators are presented as a tornado plot in Figure 54 and Figure 55. The most influential parameters were the discount rate for outcomes and costs, the progression-free health state utility value and the progression-free health state costs.

Figure 54: Tornado plot (ICER) of selpercatinib versus lenvatinib – *RET* fusion-positive TC (at selpercatinib PAS price)

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

Figure 55: Tornado plot (ICER) of selpercatinib versus BSC – *RET* fusion-positive TC (at selpercatinib PAS price)

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

B.3.11.3 Scenario analysis

In addition to the DSA and PSA, a number of scenario analyses were explored in which model assumptions or parameters were altered. Pairwise probabilistic results of the scenario analyses for *RET*-mutant MTC are presented in Table 103, and for *RET* fusion-positive TC Table 104 (at selpercatinib PAS price).

Table 103: Scenario analyses (pairwise, probabilistic) for the *RET*-mutant MTC population (at selpercatinib PAS price; including 1.2x severity modifier)

Scenario	Base case	Scenario analysis	Incremental costs	Incremental QALYs	ICER (£/QALY)
Selpercatinib versus cabozantinib: base case			[redacted]	[redacted]	**29,738**
PFS extrapolation	Loglogistic (all treatment arms)	Gamma	[redacted]	[redacted]	31,118
		Spline knot 1	[redacted]	[redacted]	34,437
OS extrapolation	Stratified Weibull (all treatment arms)	Stratified gamma (all treatment arms)	[redacted]	[redacted]	29,652
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	28,954
Drug wastage	No drug wastage is assumed	Drug wastage is assumed	[redacted]	[redacted]	23,952
Selpercatinib versus BSC: base case			[redacted]	[redacted]	**40,184**
PFS extrapolation	Loglogistic (all treatment arms)	Gamma	[redacted]	[redacted]	38,436
		Spline knot 1	[redacted]	[redacted]	41,051
OS extrapolation	Stratified Weibull (all treatment arms)	Stratified gamma (all treatment arms)	[redacted]	[redacted]	39,949
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	39,533
Drug wastage	No drug wastage is assumed	Drug wastage is assumed	[redacted]	[redacted]	40,276

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

Table 104: Scenario analyses (pairwise, probabilistic) for the *RET* fusion-positive TC population

Scenario	Base case	Scenario analysis	Incremental costs	Incremental QALYs	ICER (£/QALY)
Selpercatinib versus lenvatinib: base case			[redacted]	[redacted]	**34,620**

PFS extrapolation	Stratified Weibull (all treatment arms)	Exponential (all treatment arms)	[redacted]	[redacted]	37,186
OS extrapolation	Piecewise exponential (all treatment arms)	Weibull	[redacted]	[redacted]	32,355
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	31,998
Selpercatinib versus BSC: base case			[redacted]	[redacted]	**43,067**
PFS extrapolation	Stratified Weibull (all treatment arms)	Exponential (all treatment arms)	[redacted]	[redacted]	44,884
OS extrapolation	Piecewise exponential (all treatment arms)	Weibull	[redacted]	[redacted]	41,382
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	41,357

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

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B.3.11.4 Summary of sensitivity analyses results

The results of the sensitivity analyses demonstrate that the model is robust to variation. The DSA results identified a small number of key influential parameters – namely the discount rate for outcomes and costs (which represent known inputs), and the progression-free health state utility value and costs – with all scenarios with the exception of discount rates resulting in minimal changes to the ICERs considered. In addition, the results of the scenario analyses demonstrate that there is minimal uncertainty surrounding the base case cost-effectiveness estimate for selpercatinib versus the relevant comparators in each population. For all scenario analyses conducted, the ICER increased by a maximum of ~£5,000 per QALY, with some scenario analyses resulting in a reduction to the ICER.

B.3.12 *Subgroup analysis*

No further subgroup analyses were carried out beyond the analysis of 'adults and people aged 12 years and over with advanced RET fusion-positive TC with who require systemic therapy (and who have not previously received systemic therapy)' and 'adults and people aged 12 years and over with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy (and who have not previously receive 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

B.3.13 *Benefits not captured in the QALY calculation*

If recommended, selpercatinib will be the first RET-receptor kinase inhibitor to become available as a first-line treatment for patients with advanced *RET* fusion-positive TC and advanced *RET*-mutant MTC in the UK. Currently, these patients receive the same treatments as those without recognised oncogenic markers, which consists of MKIs (cabozantinib for RET-mutant MTC and lenvatinib for *RET* fusion-positive TC). As well as poor efficacy, MKIs are associated with numerous off-target AEs, resulting in detrimental toxicity profile and poor tolerability. As such, availability of a targeted treatment earlier in the treatment pathway would provide a substantial benefit to patients with advanced *RET* fusion-positive TC and advanced *RET*-mutant MTC, by allowing them to not receive toxic treatments.

In addition, for patients ineligible for currently available treatments who presently receive BSC, selpercatinib would represent the first available treatment. This is particularly relevant as selpercatinib would offer a treatment option for patients aged between 12 and 18 years with *RET*-mutant MTC and *RET* fusion-positive TC, who are ineligible for the therapies currently available in the UK; as such, these patients currently only receive BSC. The availability of a novel treatment for those who can presently have no active treatment options may offer hope to patients and their families of delayed disease progression and improved survival. This benefit is not captured in the QALY calculations.

As noted above, selpercatinib offers a treatment for adolescent patients with *RET*-mutant MTC and *RET* fusion-positive TC, who are ineligible for the therapies currently available in the UK. As part of TA742, the committee acknowledged the devastating impact of the disease on children and young people with *RET*-altered thyroid cancer and that benefits to carers had not been captured in the economic model. Benefits to carers are likely to be an important advantage for selpercatinib in this appraisal that cannot be robustly captured within the QALY.

B.3.14 *Validation*

The model methodology was designed to align with NICE's preferred methods. The model was built to align with the NICE reference case,[94] and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%. The model structure is closely aligned with the model used in previous NICE appraisals in thyroid cancer (TA516[24], TA535[25] and TA742).[2]

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 thyroid cancer, as part of the development of the original cost-effectiveness model used as part of TA742.[2] The cost-effectiveness model for this appraisal is largely consistent with the model utilised as part of TA742, with updates required to incorporate the revised data for selpercatinib and comparators in this appraisal. As the model is largely consistent with the model utilised as part of TA742, full validation of the model was not conducted as part of this appraisal, but the updated clinical data and other key aspects of the model were discussed with UK clinical experts in a subsequent round of validation conducted as part of this appraisal.[2, 3]

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 previous economic evaluations have been performed in *RET*-altered TC for patients who have not previously received systemic treatment, cross validation was not possible.

Clinical expert opinion

As part of TA742, expert clinical input was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted

by the model. As part of this appraisal, a subsequent round of clinical expert feedback was conducted during teleconference calls that were attended by two Lilly representatives and two external consultancy representatives. The interviews were conducted virtually in September 2023, with the interviews lasting one hour each.

B.3.15 *Interpretation and conclusions of economic evidence*

B.3.15.1 Summary of the cost-effectiveness evidence

The cost-effectiveness of selpercatinib as a treatment for advanced *RET*-mutant MTC in patients who require systemic therapy (and have not previously receive systemic therapy) was evaluated versus cabozantinib and BSC, with cabozantinib representing the primary comparator. For patients with advanced *RET* fusion-positive TC who require systemic therapy (and have not previously received systemic therapy), the cost-effectiveness of selpercatinib was evaluated versus lenvatinib and BSC, with lenvatinib representing the primary comparator.

For *RET*-mutant MTC, the results of the pairwise probabilistic cost-effectiveness analysis demonstrate that the total costs associated with selpercatinib (at PAS price), cabozantinib and BSC are £[redacted], £89,639 and £17,022, respectively. The total QALYs associated with selpercatinib, cabozantinib and BSC are [redacted], 2.11 and 1.51, respectively. The resulting pairwise ICERs are £29,738 per QALY for selpercatinib versus cabozantinib, and £40,184 per QALY for selpercatinib versus BSC.

For RET fusion-positive TC, the results of the pairwise probabilistic cost-effectiveness analysis demonstrate that the total costs associated with selpercatinib (at PAS price), lenvatinib and BSC are £[redacted], £96,451 and £16,006, respectively. The total QALYs associated with selpercatinib, lenvatinib and BSC are [redacted], 2.62 and 1.27, respectively. The resulting ICERs for selpercatinib versus lenvatinib, and selpercatinib versus BSC are £34,620 and £43,067.

The PSA and DSA analyses demonstrated that the model is robust to variation. The DSA results identified a small number of key influential parameters – namely the discount rate for outcomes and costs, and the progression-free health state utility value and costs; while the ICER increased by a maximum of ~£5,000 per QALY, with some scenario analyses resulting in a reduction to the ICER. Overall, selpercatinib is associated with substantial QALY gains and would be a valuable treatment for patients who otherwise face a severe unmet need and a poor prognosis.

B.3.15.2 Strengths and limitations of the analysis

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%. The model structure was deemed appropriate for this decision problem, as it captures the clinical benefits associated with selpercatinib and aligns with previous NICE evaluations in advanced TC and MTC.[2, 25]

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. A number of parameters were sourced from LIBRETTO-001, a methodological robust clinical trial in the patient population of interest to this submission. Where inputs were not available from LIBRETTO-001, inputs and assumptions from

previous cost-effectiveness analyses and NICE evaluations in advanced thyroid cancers were used.

While LIBRETTO-001 provides evidence for the efficacy and safety of selpercatinib as a treatment for advanced RET-altered TC and MTC, it is a single-arm trial and no direct head-to-head data were available for selpercatinib versus relevant comparators. As such, relatively efficacy estimates are based on ITCs, namely unanchored MAICs and naïve ITCs. Although the ITCs were conducted using robust methodology in accordance with NICE DSU TSD 14, the use of indirect comparison techniques inherently results in a degree of parameter uncertainty in the relative effectiveness estimates. In addition, due to small sample sizes in the LIBRETTO-001 population and data availability for the comparator populations, ITCs informing the economic analysis involved the any-line MTC and any-line TC populations from LIBRETTO-001, which may introduce a further degree of uncertainty. However, results from the ITCs demonstrate that selpercatinib is associated with a statistically significant and clinically meaningful treatment benefit, in terms of PFS and OS, compared with all comparators, and extensive scenario analyses have been conducted to explore the impact of any uncertainty in the survival estimates.

B.3.15.3 Conclusions

For patients with advanced *RET*-mutant MTC and *RET* fusion-positive TC who require systemic therapy (and have not previously received systemic therapy), selpercatinib would provide a targeted treatment option that drives deep and durable responses, with substantially improved PFS and OS. Moreover, selpercatinib provides a more tolerable treatment option that would be available to a broader range of patients, including those aged 12–17 with *RET*-mutant MTC and *RET* fusion-positive TC who currently have no active treatment options. The results of the economic analysis demonstrate that selpercatinib would introduce substantial QALY benefits compared to the current treatments in UK clinical practice, and provide patients who otherwise face a poor prognosis with an effective alternative treatment option.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for untreated advanced thyroid cancer with *RET* alterations [ID6132]

Summary of Information for Patients (SIP)

October 2023

File name	Version	Contains confidential information	Date
ID6132_Selpercatinib_NICE_SIP_FINAL_27Oct23_noCON	Final	Yes	27/10/23

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic name: Selpercatinib; **Brand name:** Retsevmo®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

In this submission, selpercatinib (Retsevmo®) will be used to treat two patient populations:

- Patients 12 years and older with **advanced, rearranged during transfection (*RET*) fusion-positive thyroid cancer** (TC), who require cancer treatment and have not received any previous **systemic cancer treatments**
- Patients 12 years and older with **advanced, *RET*-mutant medullary thyroid cancer** (MTC), who require cancer treatment and have not received any previous systemic cancer treatments

Please note that further explanations for the phrases highlighted in **black** at first instance are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **green**.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state

this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence that sets out the conditions for the use of a treatment based on evidence for its safety and effectiveness. Marketing authorisation for selpercatinib for the **treatment** of RET-mutant MTC in patients who have not received any pervious systemic cancer therapy was granted by the **Medicines and Healthcare products Regulatory Agency** (MHRA) in February 2023. Marketing authorisation for selpercatinib for the treatment of *RET*-fusion positive TC in patients who have not received any previous systemic cancer therapy is anticipated in 2024 from the MHRA. However, this is pending approval from the MHRA. More details can be found in **Document B, Section B.1.2** of the company submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

N/A

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The conditions that selpercatinib is intended to treat are advanced *RET* fusion-positive TC and advanced *RET*-mutant MTC in people that require cancer treatment and have not previously received treatment for their cancer

What is TC and MTC?

TC and MTC are cancers which affect the **thyroid gland**. The thyroid is a small gland at the base of the neck. It releases substances called **hormones** into the blood, which travel to different parts of the body. Hormones control many key bodily functions, including heart rate and **metabolism** (how cells make energy required for a person to grow, heal and stay healthy).[1]

There are five main types of cancer that affect the thyroid gland. Four of these are collectively referred to as types of TC:

- Papillary TC (PTC)
- Follicular TC (FTC)
- Hürthle cell TC
- Anaplastic TC (ATC)

TCs make up more than nine in every 10 of cancers of the thyroid gland.[2]

MTC is the fifth type of cancer that affects the thyroid gland. MTC arises from a different type of cell compared to TCs, and MTC is thought to be a different kind of cancer to TC. As well as the symptoms caused by TC, MTC can cause additional symptoms.[3, 4]

More information the symptoms of TC and MTC can be found below.

RET alterations in TC and MTC

Genes contain the instructions on how to make **proteins** in the cell. The proteins help cells to work properly and stay healthy. However, genetic changes in genes can lead to proteins that do not work normally. These changes can sometimes cause diseases, such as cancer. Genes that have been changed and can cause cancer are called **oncogenes**.

Changes in a gene called *RET* can occur. The *RET* gene contains instructions for making a protein called RET receptor tyrosine kinase. This is a protein everyone has and is important for a healthy and normal life. Changes in the *RET* gene can mean that this protein does not work normally. In some cases, these changes can cause cancer. Changes in the *RET* gene can cause many different types of cancer, including TC and MTC. These are known as ***RET*-altered cancers**. These changes in the *RET* gene are called either ***RET* fusions** or ***RET* mutations**. These can lead to *RET* fusion-positive TC and *RET*-mutant MTC.

Signs and symptoms of TC and MTC

Most people with TC and MTC do not show any signs or symptoms. These cancers are often found by hospital imaging tests (for example **computed tomography** [CT] **scans** and **magnetic resonance imaging** [MRI]) performed for another reason. However, signs of TC can include:[4, 5]

- A lump at the base of the neck
- Pain or tenderness around the neck or ears
- A constant hoarse voice
- A sore throat

- Difficultly in swallowing or breathing

As well as these symptoms, MTC can also cause additional symptoms. These include:[6]

- Diarrhoea (loose or watery stools)
- The skin on the face to become red
- Bone pain
- **Fatigue** (tiredness)
- Weight loss

How many people have TC and MTC?

In the UK, there are approximately 3,900 new cases of TC and MTC each year. These make up about one in every 100 of all new cancer cases in the UK.[7] TC and MTC can affect anyone from children to the elderly, but it is most common in people between the ages of 65 to 69 years. Women are more likely to develop TC and MTC than men. Seven in every 10 cases of TC and MTC in the UK occur in females.[7, 8]

Life expectancy

TC and MTC affect people differently. For some people their cancer will not impact their survival. However, for others, their **life expectancy** is reduced. This means the length of time they are expected to live is shortened. The survival of people with TC and MTC often depends on the type of cancer they have and how advanced their cancer was when it was **diagnosed**. For more information on the stages of cancer see **Section 2b**.

Patients who are **diagnosed** with advanced (**Stage IV**) TC and MTC are expected to live for a reduced length of time compared to patients with earlier stages of TC and MTC.

- 74 out of 100 (74%) people with advanced PTC (the most common type of TC) survive their cancer for five years after diagnosis.[9]
- 67 out of 100 (67%) of people with advanced FTC survive their cancer for five years after diagnosis.[9]
- 43 out of 100 (43%) of people with advanced MTC survive their cancer for five years after diagnosis.[9]
- 4 out of 100 (4%) of people with ATC survive their cancer for five years after diagnosis. [9]

Impact of *RET* alterations on survival

Changes in the *RET* gene in TC do not always impact a patient's survival. Some patients with TC with *RET*-fusions may not live as long as patients with TC without changes in *RET*. However, this is not always the case and patients with *RET*-fusion positive TC can live as long as patients with TC and no changes in *RET*. For patients with MTC, however, changes in *RET* often mean a shorter life expectancy. MTC with *RET*-mutations is more aggressive than MTC without changes in *RET*. Therefore, these patients have a worse prognosis and shorter life expectancy.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Most often TC and MTC are diagnosed before a patient starts showing symptoms of the condition. The cancer is usually found during medical tests for another reason.[4] Sometimes people with TC and MTC are already showing signs and symptoms of their condition when they are diagnosed. The symptoms of TC and MTC are similar, but MTC can also include additional symptoms. For more information see **Section 2a**.

In patients with visible symptoms, doctors will take a sample of cells (by a process called aspiration) or a small sample of tissue (called a biopsy) from the thyroid or neck **lymph nodes**.

A biopsy is a small procedure or operation that involves removing some or all of the swollen lymph node, which is then studied in a laboratory. Aspiration is a small procedure that involves removing some cells from the thyroid gland through a small hollow needle. The cells are then sent to be tested in a laboratory.

The cell or tissue sample will be sent to the laboratory to see whether the patient has TC or MTC. Sometimes blood tests will also be needed to confirm that a patient has MTC. If TC is confirmed, the doctor will try to understand what type of TC it is. To do this more tests, including imaging tests and blood tests are needed.

Doctors will also use these tests to work out how advanced the disease is. This is called the cancer stage. Determining the type and stage of cancer a patient has can help predict how the disease will progress over time. It also helps determine the best treatment for a patient and predict how a patient will respond to treatment.

RET testing

Some treatments for TC and MTC are only given to patients that have changes in specific genes. After determining if a patient has TC or MTC, the doctor will do a test to determine if a patient has change in specific genes.

Selpercatinib is a new drug to treat *RET*-altered TC and MTC. For more information see **Sections 2a and 3a**. Before a patient can be given selpercatinib, the doctor will need to know if they have a change in their *RET* gene. To find this out a doctor will perform a biopsy to take a small sample of tissue. This sample will then be studied by scientists in the laboratory. By performing tests, the scientists will find out if the cancer is due to changes in the *RET* gene (*RET*-altered).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Differentiated thyroid cancer (DTC)

More than 90 out of 100 (90%) of TCs are differentiated thyroid cancer (DTC).[2] Long-term survival for these patients is good, with 84 out of 100 (84%) patients with TC (including all stages of disease) living for 10 years after their diagnosis. For these patients the aim of treatment is to stop the cancer coming back. This needs to be balanced with avoiding any unneeded surgeries or side-effects of treatment.

Surgery and radioactive iodine

For patients with DTC, the first treatment will usually be a type of surgery called **thyroidectomy**. There are two types of thyroidectomy:

- **Partial thyroidectomy**, where some of the thyroid gland is removed.
- **Total thyroidectomy**, where all of the thyroid gland is removed. Patients can also have a near-total thyroidectomy, where most, but not all of the thyroid gland is removed.

After a total or near-total thyroidectomy, the cancer will then be treated with radioactive iodine therapy, also called **radioactive iodine ablation**.

For some patients, between five and 20 out of 100 (5–20%), surgery is not an appropriate treatment. This is because their cancer has spread from the thyroid gland to different parts of the body. These patients should be treated with radioactive iodine therapy.[10]

Radioactive iodine therapy (radioactive iodine ablation) is a form of **radiotherapy**. It uses a type of iodine that is radioactive (Iodine 131). Patients will usually take radioactive iodine as a capsule or drink. The radioactive iodine then enters the blood and travels around the body. The thyroid gland takes up and stores most of the iodine in the body. This means that the radioactive iodine has little effect on other cells in the body. The TC cells take up the radioactive iodine and the radiation destroys the cancer cells.

Radioactive iodine therapy can be an effective treatment for DTC. Unfortunately, for between five and 15 out of 100 (5–15%) patients their cancer is too advanced and radioactive iodine therapy does not work.[11]

In the UK, lenvatinib and sorafenib are the only treatments currently available if radioactive iodine therapy does not work. However, almost all patients currently receive lenvatinib, rather than sorafenib. These two treatment options are called **multi-kinase inhibitors** (MKIs). They are often taken as tablets. MKIs are systemic therapies that work by blocking proteins called kinases. This stops the cancer from growing and spreading. However, lenvatinib and sorafenib are only available for adult patients (18 years old and older), This means that patients with advanced TC aged 12–17 years old can only receive **best supportive care** (BSC). BSC is when a patient is given medicines to reduce pain and make them a comfortable as possible. BSC does not treat the cancer.

MKIs often lead to lots of side effects which can have a serious impact on a patient's physical health, health-related **quality of life** (HRQoL) and mental health.[12] This can mean patients need to visit their doctor or hospital more regularly to treat the side effects.[11, 13] For many patients the side effects are so bad that they have to pause or stop treatment with MKIs, often leaving BSC as the only option.

If a patient with DTC needs more treatment after receiving their first systemic cancer therapy, (**second-line treatment**), selpercatinib can be an option. Selpercatinib is already available through the **Cancer Drugs Fund (CDF)** as a second-line treatment for advanced *RET*-altered TC and MTC. For more information on selpercatinib see **Sections 3**.

ATC

Treatment options for patients with ATC are currently very limited. For some patients with ATC, surgery may be a suitable option. After surgery, **chemotherapy** and **external beam radiotherapy** may be used to destroy any cancer cells that were not removed by surgery. Selpercatinib is currently available through the CDF for patients with ATC who have not previously received any systemic cancer therapies.[14]

Chemotherapies work by destroying cells that grow and multiply quickly, such as cancer cells. However, other cells in the body that multiply quickly (such as hair and skin cells) are also affected by chemotherapy. Therefore, these treatments often lead to side effects such as hair loss.[15] Chemotherapies are sometimes given by an intravenous drip or injection into the blood, which requires patients to receive these treatments in hospital.[16]

Radiotherapies works by using high doses of radiation to destroy cancer cells and shrink cancers. Low doses of radiation are used in x-rays to see inside your body, for example when looking at a broken bone. External beam radiotherapy uses a large machine, which requires a patient to go to hospital for treatment. It is a **local therapy**, which means it only targets the part of your body where the cancer is. However, radiation does not only kill the cancer cells. It can also harm healthy cells which can cause side effects.

There are some patients whose cancer is too advanced and chemotherapy and external beam radiotherapy do not work. For these patients, there are no treatment options recommended by NICE, and the only treatment option is BSC.[10]

If a patient with ATC needs more treatment after receiving their first systemic cancer therapy, (second-line treatment), selpercatinib is available through the CDF. For more information on selpercatinib see **Sections 3**.

MTC

The long-term outlook for patients with MTC is worse than that of patients with DTC. However, if treatments for MTC are effective, a patient's outlook can be good.

Patients with MTC will usually have surgery. Most patients will have either a partial or total thyroidectomy. Some patients may also receive another surgery called a selective neck dissection. This is the removal of lymph nodes that the cancer could spread to. In patients with MTC, where surgery is not an option, radiotherapy may be used.[10]

Cabozantinib is another MKI, a type of systemic therapy. In the UK, cabozantinib is the only treatment option available for patients with either advanced MTC or MTC that has spread to other parts of the body that cannot be treated with surgery.[17] However, cabozantinib can only be given to adult (over 18 years old) patients. This means for patients with advanced MTC aged 12–18 years old, BSC is the only option.

For patients that cannot be treated with surgery, radiotherapy or cabozantinib, BSC is the only treatment option. However, the majority of patients with advanced MTC currently receive cabozantinib, rather than BSC.

If a patient with MTC needs more treatment after receiving cabozantinib (second-line treatment), selpercatinib is available through the CDF. For more information on selpercatinib see **Sections 3**.

Comparators to selpercatinib

For patients with TC, the comparators to selpercatinib are lenvatinib and BSC. Lenvatinib is considered the main comparator as the majority of patients with TC receive lenvatinib.

For patients with MTC, the comparators to selpercatinib are cabozantinib and BSC. Cabozantinib is considered the main comparator as the majority of patients with MTC receive cabozantinib.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Lilly have collected patient-based evidence through the HRQoL measures in the selpercatinib trial. The outcomes of the HRQoL measures from the key trial (LIBRETTO-001) are presented in **Section 3e**. The section summarises some of the key considerations from published literature about the impacts of TC and MTC on patients.

Impact of TC and MTC and current treatments on patients

As discussed in **Section 2a**, the key symptoms of TC and MTC are a lump at the base of the neck, pain around the neck or ears, a constant hoarse voice, a sore throat and difficulty swallowing or breathing.[4, 5] In addition, patients with MTC can experience diarrhoea, the skin on the face becoming red, bone pain, tiredness and weight loss.[6] Some symptoms, such as severe diarrhoea, pain and fatigue can impact a patient's physical and mental wellbeing.[18, 19]

Studies have shown that patients with PTC have a poorer HRQoL than the general population.[18] Additionally, TC and MTC can have a negative impact on a patient's mental health, with many patients experiencing concerns about their physical and mental wellbeing, the cancer returning, the prospect of more surgeries and how the disease will affect their ability to work.[20] Patients can also suffer from increase anxiety and depression.[21]

While TC is generally diagnosed in people between the ages of 65 to 69 years, it can also occur during early adulthood. These patients can suffer from a more aggressive form of cancer and have a worse outlook (prognosis). This can have a serve impact on these patients quality of life and mental health.[12]

Currently, there is not much information on how *RET* fusion-positive TC and *RET*-mutant MTC impact patients' HRQoL. This is because most studies look at TC and MTC, with very few focussing only on *RET* fusion-positive TC and *RET*-mutant MTC.

The treatment options currently available for patients with advanced *RET*-fusion positive TC and advanced *RET*-mutant MTC are limited to poorly **tolerated** MKIs. These treatments can only slow down the cancer and often lead unpleasant side-effects and issues after surgery. This can badly affect a patient's quality of life and mental health.[12]

TC and MTC can be costly for both the patient and health system because of its impact on a patient's ability to work and healthcare resources. Because of their symptoms and treatments patients often need to take time off work.[20] This can mean their income is reduced or lost completely. This can be extremely worrying for a patient and lead to a poorer quality of life. Patients who have difficulties with work due to their cancer, can find this impacts their symptoms, experiencing worse fatigue and pain.[22]

Further information of the impact of TC and MTC on patients can be found on this website, which details some stories from patients with TC and MTC:
https://www.butterfly.org.uk/patient-experiences/your-experiences/

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

About selpercatinib

Selpercatinib is a treatment for TC and MTC that is given as a tablet. Selpercatinib is a type of treatment called a small molecule inhibitor of the RET receptor tyrosine kinase. This means that selpercatinib works by blocking (inhibiting) a type of protein called RET receptor tyrosine kinases. By doing this it can stop the growth and spread TC and MTC that have altered RET proteins.

Unlike other treatments, such as MKIs, selpercatinib is a type of **targeted therapy**. This means that selpercatinib blocks RET receptor tyrosine kinases only. MKIs are not targeted which means that they block many proteins. This is why MKIs cause many different side effects.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable – selpercatinib will not be used with any other medicines for treating TC and MTC.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Selpercatinib is taken as a tablet. This means patients can receive treatment at home. This can save patients and caregivers money and time, compared to a treatment that needs to be received in hospital, as patients will not need to travel to the hospital for treatment. It can also provide a sense of normality while being treated.[23]

The dose of selpercatinib that a patient takes is based on their body weight:

- Patients who weigh less than 50 kg will take a total dose of 120 mg (two tablets), twice a day.
- Patients weighing 50 kg or more will take two tablets twice a day, for a total dose of 160 mg.

Patients will continue to receive treatment with selpercatinib until the disease gets worse or the **side effects** from the medicine are too severe to manage.[23]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The main clinical trial that provides evidence on the efficacy and safety of selpercatinib as a treatment for *RET* fusion-positive TC and *RET*-mutant MTC is LIBRETTO-001. A summary of the key information about the trial is provided below. More information can be found in **Document B** in **Section B.2.2** and the **Appendix N**.

Another clinical trial called LIBRETTO-531, that is currently ongoing, provides some additional evidence for selpercatinib as a treatment for RET-mutant MTC. This is a Phase III trial comparing the safety and efficacy of selpercatinib with two MKIs (cabozantinib or vandetanib [cabozantinib/vandetanib]) for treating *RET*-mutant MTC. The first data from LIBRETTO-531 have only been published very recently, and are from an interim analysis (very early **data cut**) of the trial.[24] As the data are very new, this means that LIBRETTO-531 only provides supportive data for this submission, and LIBRETTO-001 represents the main clinical evidence.

LIBRETTO-001 (Clinical trial number: NCT03157128)[25, 26]

LIBRETTO-001 is a **Phase I/II trial**. The aim of the trial is to study the efficacy and safety of selpercatinib as a treatment for *RET*-altered cancers. Part of this trial looks at the efficacy and safety of selpercatinib as a treatment for *RET*-altered TC and MTC. The trial is ongoing at hospitals around the world in Europe, North America, Asia and Australia. To be able to take part in the trial patients have to be 12 years old or older and have advanced TC with *RET* fusions or advanced MTC with *RET* mutations. In total, 143 patients with MTC with *RET* mutations (who have not previously received cabozantinib or vandetanib) and 24 patients with TC with *RET* fusions (who have not received any previous systemic cancer therapy) have taken part in the study.

Some of the key results from this trial are explained in more details in the sections below.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Clinical trial results

LIBRETTO-001

The LIBRETTO-001 clinical trial studied selpercatinib for the treatment of patients with TC and MTC who have not received systemic cancer therapy. LIBRETTO-001 is a Phase I/II trial. This means that it first tests how much of selpercatinib is safe to give people with TC and MTC (Phase I). Then it tests how well selpercatinib works as a treatment for TC and MTC (its **efficacy**), as well understanding more about how safe the drug is (Phase II). The trial also looked at the impact of selpercatinib on patients' quality of life.

The results in clinical trials are called **outcomes** (or endpoints). Clinical trials have primary outcomes. These are the main result at the end of a clinical trial, which measures to see if the treatment works. As well as the primary outcome, clinical trials also collected other results, known as secondary outcomes. Results presented below are for patients with *RET*-mutant MTC who had not previously received cabozantinib or vandetanib or patients with *RET* fusion-positive TC who had not previously received any systemic therapy.

The main outcome of the LIBRETTO-001 clinical trial was **objective response rate** (ORR). ORR is the proportion of patients whose cancer has either gone away (**complete response**) or shrunk by at least 30% (a **partial response**). ORR in LIBRETTO-001 was 83% for patients with *RET*-mutant MTC and 96% for patients with *RET* fusion-positive TC.[27]

Other outcomes in the LIBRETTO-001 study included **duration of response** (DOR). DOR is how long a cancer continues to respond to treatment without the cancer growing or spreading. Selpercatinib resulted in a DOR of at least two years in 84% of patients with *RET*-mutant MTC. For patients with *RET* fusion-positive TC, treatment with selpercatinib resulted in a DOR of at least two years in 91% of patients.[27]

Progression-free survival (PFS) was another outcome. PFS is the length of time between starting a cancer treatment and signs that the cancer has started to progress, or the patient's death. In the LIBRETTO-001 study, 83% of patients with RET-mutant MTC survived without

their disease getting any worse for at least two years after their treatment started respectively. For patients with *RET* fusion-positive TC, 95% of patients survived without their disease getting any worse for at least two years after their treatment started.[27]

Limitations of LIBRETTO-001

During a clinical trial there are often factors in the way that the study is carried out that may impact the results. These are known as limitations. It is important to think about the impact these limitations can have on the results of a clinical trial.

In LIBRETTO-001, only a small number of patients were involved, with the number of patients with *RET* fusion-positive TC being very small. This is a limitation of the study, as it means there is some uncertainty about the efficacy and safety of selpercatinib.

LIBRETTO-001 is a **single-arm study**. This means that selpercatinib was not compared with any other treatments in the trial (**control drugs**). To understand how selpercatinib compares with other available therapies using the results from LIBRETTO-001, an **indirect treatment comparison** (ITC) is needed.

LIBRETTO-531[24]

PFS results are also available from the LIBRETTO-531 study. While the data are still very new, they suggest that selpercatinib substantially improves PFS compared to cabozantinib or vandetanib. After one year, 86.8% of patients receiving selpercatinib survived without their disease getting any worse, compared with 65.7% of patients receiving cabozantinib or vandetanib. Treatment with selpercatinib was estimated to reduce the risk of disease progression or death by 72% compared to cabozantinib or vandetanib.

Selpercatinib compared with other available therapies

The LIBRETTO-001 trial was a single-arm trial and therefore did not directly compare selpercatinib to existing treatments in UK clinical practice, and the results of the head-to-head LIBRETTO-531 trial are still very new and from an early data cut off.

As such, it was necessary to perform indirect treatment comparisons between selpercatinib in LIBRETTO-001 and each of the relevant comparators. An ITC was also conducted for selpercatinib versus sorafenib for completeness. An ITC enables the outcomes of a trial for one drug to be compared to the outcomes of a trial for another drug, in order to assess the relative effectiveness of one drug over another when they have not been directly compared in the same trial.

For patients with TC, the results of the ITCs showed that treatment with selpercatinib led to improvements in PFS and OS compared with lenvatinib, sorafenib and BSC. Similarly, for patients with MTC, the results of the ITCs showed that treatment with selpercatinib led to significant improvements in PFS and OS compared with cabozantinib and BSC.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In LIBRETTO-001, information was collected about the HRQoL of patients with MTC and TC.

HRQoL was measured by:

- The European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C3): a questionnaire developed to assess the HRQoL of adults with cancer.
- Bowel diaries**:** a diary to be filled in by patients about their bowel habits. Diarrhoea is a symptom known to impact the quality of life of patients with MTC. The aim of a bowel diary is to assess the impact diarrhoea has on a patient's HRQoL and if it improves with treatment.

EORTC-QLQ-C3 data were collected for patients with MTC and TC. Bowel diaries were only collected for patients with MTC.

EORTC-QLQ-C30 was used to measure how many patients experienced improved, stable or worsened quality of life. Treatment with selpercatinib led to improvements in quality of life for 35% of patients with *RET*-mutant MTC. 46% of patients with MTC experienced no change in their quality of life. For patients with *RET* fusion-positive TC, selpercatinib led to improvements in quality of life for 17% of patients. 58% of patients with TC experienced no change in their quality of life.[28]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Side effects are the unwanted effects of a treatment. Different drugs can cause different side effects. The same drug can cause different side effects in different people. This means it can be difficult to predict what side effects a patient will get.

Selpercatinib is a targeted therapy for the RET receptor kinase. However, healthy cells also have RET receptor kinase. This means that selpercatinib can also affect healthy cells. Because of this, patients treated with selpercatinib will experience some side effects.

In clinical trials, information relating to the safety of a treatment is collected in the form of adverse events (AEs). AEs are any unfavourable and unintended signs associated with treatment, although it is not always clear whether these are directly caused by the treatment or not.

LIBRETTO-001[27]

In LIBRETTO-001, information on AEs associated with selpercatinib was collected for:

- Patients with *RET*-mutant MTC

- Patients with *RET* fusion-positive TC

AEs experienced by patients with *RET*-mutant MTC and patients with *RET* fusion-positive when treated with selpercatinib were similar. The most common AEs experienced by patients receiving selpercatinib were:[27]

- Nausea (feeling sick)
- Fatigue (tiredness)
- Diarrhoea (loose or watery stools)
- Hypertension (high blood pressure)
- Dry mouth
- Abdominal pain
- Constipation

In clinical trials, AEs are graded on a scale from 1–5 (most clinical trials focus on Grade 3 or higher events):[29]

- Grade 1–2: mild AEs that generally do not impact patients significantly and are not dangerous
- Grade 3–4: serious AEs that interfere with patients' ability to do basic things. They may also mean that patients need to be seen by their doctor for medical intervention
- Grade 5: fatal AEs

The most common AEs that were Grade 3 or higher when treated with selpercatinib were similar for both patients with MTC and patients with TC. These included:[27]

- Hypertension (high blood pressure)
- Diarrhoea
- Abdominal pain

Certain AEs that were Grade 3 or higher were more common in patients with MTC when treated with selpercatinib:[27]

- Alanine aminotransferase (ALT) increase (the amount of a protein called ALT in your blood is higher than normal. This can mean there is damage to your liver)
- Aspartate aminotransferase (AST) increase (the amount of a protein called AST in your blood is higher than normal. This can mean there is damage to your liver)

For patients treated with selpercatinib, the adverse events were usually manageable with appropriate monitoring and measures such as delaying treatment and/or providing additional medical support.

Some patients had to have their dose of selpercatinib reduced or withheld. Withholding treatment is when a doctor decides not to give a patient their planned dose of their medicine. The most common reason for withholding treatment or reducing the dose of selpercatinib was due to adverse events.

Some patients stopped treatment with selpercatinib due to AEs. For patients with RET-mutant MTC, 5% of patients stopped treatment with selpercatinib due to an AE that was related to selpercatinib. For patients with RET fusion-positive TC, 2% of patients stopped treatment with selpercatinib due to an AE that was related to selpercatinib.

LIBRETTO-531[24]

Safety data for selpercatinib versus cabozantinib/vandetanib for patients with *RET*-mutant MTC were also collected from LIBRETTO-531. At the early data cut off, the results showed that selpercatinib was associated with a more tolerable safety profile compared to cabozantinib or vandetanib. Overall, 90% of patients experienced an AE related to treatment in the selpercatinib group, compared with 98% in the cabozantinib/vandetanib group.

Patients in the cabozantinib/vandetanib group were more likely to experience grade 3 or higher AEs that were related to their treatment. 68% of patients in the cabozantinib/vandetanib group experienced a grade 3 or higher AE related to treatment, compared with 37% of patients in the selpercatinib group. Similarly, 6% of patients experienced a serious AE related to study treatment in the selpercatinib group, compared with 18% in the cabozantinib/vandetanib group.

Only 2% of patients discontinued selpercatinib due to an AE related to treatment. In contrast, 23% of patients discontinued cabozantinib/vandetanib due to an AE related to treatment.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Selpercatinib is an effective treatment for advanced *RET* fusion-positive TC and *RET*-mutant MTC, leading to substantially improved PFS and OS versus current comparators

The LIBRETTO-001 trial showed that selpercatinib is an effective treatment for patients with *RET*-mutant MTC and *RET* fusion-positive TC. Results from the trial show that over 80% of patients with *RET*-mutant MTC and 95% of patients with *RET* fusion-positive TC can live at least two years after starting selpercatinib treatment without their disease getting worse (progressing). This shows that selpercatinib is an effective treatment for patients with *RET* fusion-positive TC and *RET*-mutant MTC.

Indirect treatment comparisons showed that treatment with selpercatinib led to improvements in PFS and OS compared with lenvatinib, sorafenib and BSC (for patients with *RET* fusion-positive TC), and compared with cabozantinib and BSC (for patients with *RET*-mutant MTC).

These results are further supported by early data from the LIBRETTO-531 trial, which suggests that selpercatinib reduces the risk of PFS by 72% when compared to cabozantinib or vandetanib for patients with *RET*-mutant MTC.[24]

Selpercatinib can improve HRQoL for patients over time

Patients with MTC and TC have decreased HRQoL because of reasons including pain, fatigue and worrying about money problems.[18, 19, 22] For patients with MTC, diarrhoea can also impact their HRQoL. The LIBRETTO-001 trial showed that selpercatinib treatment led to improvements in the HRQoL for many patients.

As selpercatinib can extend the time that patients live without their disease getting worse and improve HRQoL, patients receiving selpercatinib can live longer with improved HRQoL compared with currently available treatments.

Selpercatinib results in decreased side effects compared to currently available MKIs

In the UK, the MKIs lenvatinib and sorafenib are the only available treatments for advanced *RET* fusion-positive TC. Another MKI, cabozantinib is the only treatment available for advanced *RET*-mutant MTC. As these treatments are not targeted, they can cause a wide range of serious side effects. For many patients these side effects can seriously affect their physical and mental health meaning they have to stop treatment.[13, 30] As there are currently no alternative treatment options for patients who have not received any previous systemic cancer therapy, this leaves BSC as the only option left for these patients.

Unlike the MKIs currently used in the UK, selpercatinib is a targeted treatment for both advanced *RET*-fusion positive TC and advanced *RET*-mutant MTC. This means patients experience less serious side effects with selpercatinib than with other MKIs. Therefore, patients are less likely to need to stop treatment.[31-33] Selpercatinib also provides another treatment for those patients whose only option left is BSC. Therefore, selpercatinib may solve the unmet need for an effective treatment that does not cause patients serious side effects for patients who have not received any previous systemic cancer therapy.

The availability of selpercatinib as a treatment option for patients who have not received any previous systemic cancer therapy means that patients will be able to access a safer and more effective treatment option as soon as possible in the treatment pathway, rather than needing to try MKIs first and experience disease progression before being able to receive selpercatinib.

Selpercatinib provides a treatment option for patients aged 12–17 years

Currently in the UK, cabozantinib can only be given to adult patients with advanced MTC, and lenvatinib and sorafenib can only be given to adult patients with advanced TC. Therefore, for patients under the age of 18 years old with advanced MTC or TC, BSC is the only option. In contrast to cabozantinib, lenvatinib and sorafenib, selpercatinib can be given to patients that are 12 years or older. Therefore, selpercatinib will provide the first effective treatment option for patients with *RET*-mutant MTC and *RET* fusion-positive TC aged 12–17 years old. This will address an important unmet need for these patients and represents an important benefit of selpercatinib compared to currently available treatments.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The side effects associated with selpercatinib are generally manageable with appropriate monitoring and measures such as delaying treatment and/or providing additional medical support. However, like all existing therapies for TC and MTC, some patients may experience side effects that are not manageable, and treatment may need to be temporarily or permanently stopped for some people. Selpercatinib is a targeted therapy, while MKIs are not. Therefore, for most patients, this means treatment with selpercatinib will lead to less side

effects than treatment with MKIs. Additionally, treatment with selpercatinib is less likely to be stopped due to unpleasant side effects, when compared to MKIs. For more information on targeted therapies see **Section 3a**.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

An economic analysis was performed to assess whether selpercatinib represents good value for money and a good use of resources for the NHS compared to existing treatments in UK clinical practice. The analysis was performed using an economic model. This compared the costs and benefits of the new treatment (selpercatinib) with the currently available treatments, called the comparators (lenvatinib and BSC for patients with *RET* fusion-positive TC, and cabozantinib and BSC for patients with *RET*-mutant MTC).

How the model reflects advanced *RET*-altered TC and MTC

In order to capture all of the potential costs and benefits associated with treatment with selpercatinib, the model assessed the cost-effectiveness of selpercatinib over the lifetime of patients with advanced TC and MTC.

A model structure called a **partitioned survival model**, which is a conventional approach used in across oncology models, and specifically for thyroid cancer**,** was used. The economic model was comprised of three health states: progression free (patients' disease is responding to treatment and not actively progressing), progressed (the patient's cancer has worsened) and death. These health states reflect the three potential stages of health associated with advanced TC and MTC. In the progression-free health state, patients have treatment with either selpercatinib or one of the comparators. The model did not allow people to move to an improved level of health. This reflects the progressive nature of the disease.

Modelling the impact of selpercatinib on health and QoL

The economic analysis considered how much selpercatinib extended both OS and PFS to track how many patients live without the disease worsening over time.

The PFS and OS results of the ITC were the main clinical inputs in the economic analysis. As the ITC was informed by clinical data from the relevant trials for selpercatinib and its

comparators, the model is expected to accurately reflect disease progression and the survival rate of patients treated with these therapies in UK clinical practice. As data obtained from the LIBRETTO-001 trial were limited to approximately four years, these data were extrapolated in order to cover the full lifetime horizon of the economic model (25 years). Survival curves selected for the extrapolations were informed by UK clinical experts to ensure that they accurately reflected the natural progression of the disease.

Due to the improved efficacy of selpercatinib compared to existing treatments, it is anticipated that patients receiving selpercatinib will remain progression-free for longer compared to the other treatments in the model (and hence remain in the progression-free health state of the model for longer). Patients whose disease has not yet progressed have improved HRQoL compared to patients whose disease has progressed, due to the associated worsening in symptoms with disease progression.[34] It is also anticipated that patients receiving selpercatinib will remain alive for a longer period of time compared to the other treatments in the model.

When the time spent without disease progression and alive is combined with the quality of life, both the quality and time is captured by **quality-adjusted life years (QALYs)**. The quality of life is measured using **utility values**. Utility values are generally a number between 0, which represents death, and 1, which represents perfect health. QALYs are a health outcome measure that consider both the length and the quality of life provided by a treatment. A year spent in perfect health (i.e. a utility score of 1) represents one QALY. Side effects were taken into account by lowering patients' utility values, and therefore QALYs, when they experienced a side effect.

Modelling the costs of treatments

Different costs are included in the model for the different treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of monitoring the patients whilst they receive treatment
- The costs of managing the disease
- The cost of side effects that can happen during treatment

Results of the economic analysis

The effectiveness of selpercatinib and the associated costs were modelled over a period to reflect the lifetime of patients. The resulting accumulation of costs and QALYs associated with each treatment, and the ratio between these values, indicates whether the treatments are cost effective or not. A ratio of £20,000 to £30,000 per QALY is considered cost-effective for a new treatment to be adopted by the NHS.

A **severity modifier** is a factor that takes into account the severity or impact of a disease when evaluating the cost-effectiveness of a particular treatment. In the *RET*-mutant MTC population, selpercatinib is eligible for a severity modifier when compared with cabozantinib and BSC. In the *RET* fusion-positive TC population, selpercatinib is eligible for a severity modifier when compared with BSC, but not when compared with lenvatinib.

Overall, the results of the economic analysis showed selpercatinib to be associated with increased costs and increased QALYs when compared to all treatments. For the RET-mutant MTC population, the ratio of costs and QALYs for selpercatinib compared with cabozantinib and BSC was £29,738 per QALY and £40,184 per QALY, respectively. For the *RET* fusion-positive TC population, the ratio of costs and QALYs for selpercatinib compared with lenvatinib and BSC was £34,620 per QALY and £43,067 per QALY, respectively. As stated above,

selpercatinib is eligible for a severity modifier for some comparisons and these results do not take this severity modifier into account.

It is important to note that the Company's estimation of cost-effectiveness is not the only result considered by NICE. NICE may prefer some assumptions that are different from the assumptions that the company used in their model. In addition, some comparators treatments may have confidential discounts that the Company do not have access to.

Benefits of selpercatinib not captured in the economic analysis

Selpercatinib offers a treatment for patients aged between 12 and 17 years with advanced *RET*-mutant MTC and *RET* fusion-positive TC. Treatment with selpercatinib will benefit both those with the disease and carers of children and young people with *RET*-altered MTC and TC. The benefits to carers are an important advantage of selpercatinib that is not included in the economic analysis.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Selpercatinib is a new and innovative treatment for *RET*-fusion positive TC and *RET*-mutant MTC

In the UK, treatments currently available to treat advanced *RET*-fusion positive TC are lenvatinib and sorafenib. For advanced *RET*-mutant MTC, cabozantinib is the only available treatment. However, these treatments are not targeted. Survival on current treatments is poor and they can cause many serious side effects. These side effects can impact on patient's physical and mental health and for some patients mean they cannot continue treatment. There is therefore a high unmet need for an effective and tolerable treatment option to be made available to patients with advanced *RET*-altered TC and MTC as early as possible in the treatment pathway.

Selpercatinib is a targeted therapy that works by blocking RET receptor tyrosine kinases only. This means that selpercatinib is an effective treatment and it is associated with less side effects than MKIs. The results of the ITC demonstrate that selpercatinib is more effective at delaying disease progression and patients are more likely to live longer, compared with currently available treatments. As a result, selpercatinib would represent an important advancement in the treatment of advanced *RET* fusion-positive TC and *RET*-mutant MTC.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this 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
Find more general information about the Equality Act and equalities issues here

There are no equality issues that are anticipated for the use of selpercatinib in patients with untreated advanced *RET* fusion-positive TC and *RET*-mutant MTC.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on TC:

- National Health Service's guide on thyroid cancer Thyroid cancer | Conditions | NHS (www.nhs.uk)
- Macmillan's guide on thyroid cancer Thyroid cancer | Cancer information and support | Macmillan (www.macmillan.org.uk)
- American Cancer Society's guide on thyroid cancer Thyroid cancer | Types | Cancer | American Cancer Society (www.cancer.org)
- Cancer Research UK's guide on thyroid cancer Thyroid cancer | About cancer | Cancer Research UK (www.cancerresearchuk.org)
- British Thyroid Foundation's guide on thyroid cancer Thyroid cancer leaflet | British Thyroid Foundation (www.btf-thyroid.org)

Further information on MTC:

- Macmillan's guide on medullary thyroid cancer Medullary | Thyroid cancer | Cancer information and support | Macmillan (www.macmillan.org.uk)

Further information on the LIBRETTO-001 trial:

- U.S. National Library of Medicine entry for LIBRETTO-001 trial LIBRETTO-001 trial (NCT03157128) | U.S National Library of Medicine (classic.clinicaltrials.gov)

Further information on the LIBRETTO-531 trial:

- U.S. National Library of Medicine entry for LIBRETTO-531 trial LIBRETTO-531 trial (NCT04211337) | U.S National Library of Medicine (classic.clinicaltrials.gov)

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf

- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black** in this document. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Word	Definition
Advanced cancer (thyroid cancer or medullary thyroid cancer)	Advanced is used to describe cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to other parts of the body.
Advanced RET-mutant medullary thyroid cancer	An advanced medullary thyroid cancer that is cause by a *RET* mutation.
Advanced rearranged during transfection (RET) fusion positive thyroid cancer	An advanced thyroid cancer that is cause by a *RET* fusion.
Best supportive care	A term used when there are no other options available to treat the cancer. The aim of best supportive care is to provide the patient with the best quality of life possible. By relieving any disease-related symptoms, such as pain, and making the patient as comfortable as possible. BSC does not treat the cancer.
Cancer Drugs Fund (CDF)	A source of funding for cancer treatments in England that provides temporary access to the treatment while further evidence on efficacy and safety is collected. This allows patients to access new cancer therapies more quickly. After more data are collected, the treatment may be routinely available for patients or the temporary funding may be removed for new patients.
Cell	Muscles and organs are made of small units called cells.
Chemotherapy	A type of cancer therapy that uses drugs to kill cancer cells.
Control drug	The standard (for example, another medicine or usual care) against which a medicine is compared in a study. The control can be no intervention (for example, best supportive care).
Complete response	The disappearance of all signs of cancer in response to treatment. However, this does not always mean the cancer has been cured. Also called complete remission.

Computerised tomography (CT) scan	A procedure that uses a computer and an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly.
Data cut	During a clinical trial it is very common for the researchers to analyse the data collected certain time points during the trial, before it is completed. These time points are called data cuts. This is important as it allows researchers to see if the drug is working as they predicted.
Diagnosis (diagnosed)	The process of identifying a disease or condition by carrying out tests or by studying the symptoms.
Duration of response	How long a cancer continues to respond to treatment without the cancer growing or spreading.
Efficacy	The ability of a medicine to produce a desired positive effect on your disease or illness in a clinical trial.
External beam radiotherapy	A type of radiotherapy that uses a machine outside the body to direct radiation beams at cancer to destroy it.
Fatigue	This is when you feel very tired, exhausted and lacking energy. It can be a symptom of the cancer or a side effect of treatment.
Fusion	The joining together of two genes
Gene	A gene is an inherited part of a cell in a living thing that controls physical characteristics, growth and development.
Hormones	Chemical substances that carry messages within the body to help coordinate different bodily functions.
Indirect treatment comparison	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised trial.
Life expectancy	How long a patient is expected to live.
Local therapy	A type of cancer therapy that is aimed at just at a specific location
Lymph nodes (also called glands)	Small structures in the body that trap germs and abnormal cells. Found in the neck, armpit and groin. Lymph nodes are part of the immune system.
Objective response rate	Objective response rate is the total number of people whose cancer has either gone away (complete response) or shrunk by at least 30% (a partial response).

Overall survival	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works. Also called overall survival.
Magnetic resonance imaging	A procedure that uses a computer and an medical imaging machine to make a series of detailed pictures of areas inside the body
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.
Medullary thyroid cancer	Cancer of the thyroid gland. It is cause by the abnormal growth of a type within in the thyroid gland called non-follicular C cells.
Metabolism	How cells make energy required for a person to grow, heal and stay healthy
Multi-kinase inhibitors	These are a type of targeted therapy that block proteins called kinases inside cancer cells which tell the cancer to grow.
Mutation	Our genes pick up mistakes that happen when cells divide. These mistakes are called genetic mutations. It is usual for cells to repair faults in their genes or to remove them from the body. Cancer happens when cells with genetic mutations are not repaired or removed from the body and instead multiply out of control.
Oncogenes	Genes that have been changed and can cause cancer.
Outcomes (endpoints)	Outcomes in a clinical trial are measurable changes in a patient's health or quality of life that result from a treatment.
Partial response	A decrease in the size of the cancer, or in the extent of cancer in the body, in response to treatment. Also called partial remission.
Partial thyroidectomy	A type of surgery where some of the thyroid gland is removed.
Partitioned survival model	A type of model that is used to analyse the impact of different factors on survival estimates within distinct groups of a population.
Phase 1 (also called Phase I) clinical trial	This is the first step in testing a new treatment in people. A phase I clinical trial tests: • the safety, side effects, best dose, and timing of a new treatment, • the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection), and

	• how the treatment affects the body The dose is usually increased a little at a time to find the highest dose that does not cause harmful side effects.
Phase 2 (also called Phase II) clinical trial	A study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumour or improves blood test results). Phase II clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body.
Prognosis	This gives an idea about whether the cancer can be cured and what may happen in the future.
Progression-free survival	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works. Also called progression-free survival.
Proteins	Proteins are needed for the body to function properly. They are the basis of body structures, such as skin and hair.
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Radioactive iodine ablation (also called radioactive iodine therapy)	A form of radiotherapy that uses a type of iodine that is radioactive (Iodine 131). Patients will usually take radioactive iodine as a capsule or drink.
Radiotherapy	A type of cancer therapy that uses radiations to kill cancer cells.

Rearranged during transfection (RET)	The *RET* gene contains instructions for making a protein called RET receptor tyrosine kinase.
***RET* fusions**	The joining together of two *RET* genes
***RET* mutations**	An alteration of the normal *RET* gene
***RET*-altered cancers**	Cancers that are cause by either *RET* fusions or *RET* mutations
Second-line treatment	Treatment for a disease (cancer) after the initial treatment for patients who have not received any previous systemic cancer therapy and has failed, stopped working, or has side effects that can not be put up with anymore.
Severity modifier	A factor that takes into account the severity or impact of a disease or condition when evaluating the cost-effectiveness of the treatment
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Single-arm study	A type of clinical trial where all patients receive the same medicine. The medicine is not compared with another treatment.
Stage (Stage 0–IV)	A description of how severe a disease is. Stage IV is the most severe.
Systemic cancer treatments	A type of cancer therapy that is aimed at the whole body or multiple organs, not just at a specific location.
Targeted therapy	Targeted cancer drugs work by 'targeting' the differences between a cancer cell and normal cell that help cancer cells survive and grow. As these therapies target cancer cells specifically, they limit damage to healthy parts of the body.
Thyroid cancer	Cancer of the thyroid gland. It is cause by the abnormal growth of a type within in the thyroid gland called follicular cells.
Thyroidectomy	A surgery to remove some (partial) or all (total) of the thyroid gland.
Thyroid gland	A small gland at the base of the neck, that releases substances called hormones into the blood.
Tolerated	The ability to put up with the side effects of treatment.
Total thyroidectomy	A type of surgery where all of the thyroid gland is removed. A near-total thyroidectomy is a type of surgery where most, but not all, of the thyroid gland is removed.
Utility value	A measure of health-related quality of life, typically ranging from 0 (indicating death) and 1 (indicating perfect health)

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with *RET* alterations [ID6132]

Clarification questions

30th November 2023

File name	Version	Contains confidential information	Date
ID6132_Selpercatinib TC_Company Response to Clarification_17Apr24 [CON REDACTED]	Final (Version 2)	Yes	17th April 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

LIBRETTO-001

A1. Priority question. Please provide the number (and proportion) of LIBRETTO-001 trial patients meeting the criteria set out in the table below.

The criteria listed in Table 1 are generic inclusion criteria for all cohorts of the LIBRETTO-001 trial, regardless of indication (i.e., thyroid cancer, non-small cell lung cancer [NSCLC] or the tumour-agnostic population). It was per the Investigator's discretion as to whether these criteria were fulfilled, permitting patients to be enrolled in the study, but the exact criteria fulfilled to permit enrolment was not recorded for individual patients.

However, the number of patients who progressed on prior standard therapy were presented in the Company Submission (CS), in Table 8 and Table 11, for rearranged during transfection (*RET)*-mutant medullary thyroid cancer (MTC) and *RET* fusion-positive thyroid cancer (TC) patients, respectively. Within this subset of patients, it was not recorded whether any of the additional criteria listed below were applicable. It is likely that the proportion of patients that progressed on prior standard therapy included a proportion of patients that were intolerant to standard therapy. As such, the proportion of patients in the MTC and TC patient populations who progressed on prior standard therapy or were intolerant to standard therapy are presented Table 1. These data are presented for the any-line (N=295) and cabozantinib/vandetanib naïve (N=143) MTC patient populations, and the any-line (N=65) and systemic therapy naïve (N=24) TC patient populations; these analysis sets were defined in Table 5 of the CS.

Lilly are unable to provide data for the remaining rows listed in Table 1 as these specific criteria were not collected at entry to the LIBRETTO-001 trial.

Table 1: Further details on prior standard therapies in the LIBRETTO-001 trial (MTC and TC analysis sets)

	RET-mutant MTC Cabozantinib/ vandetanib naïve (N=143)	*RET*-mutant MTC Any line population (N=295)	*RET* fusion-positive TC Systemic treatment naïve (N=24)	*RET* fusion-positive TC Any line population (N=65)
Patients who progressed on and/or were intolerant to standard therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients for whom no standard therapy exists, n (%)	NR	NR	NR	NR
Patients who were not candidates for standard therapy, n (%)	NR	NR	NR	NR
Patients who would be unlikely to tolerate standard therapy, n (%)	NR	NR	NR	NR
Patients who would be unlikely to derive significant clinical benefit from standard therapy, n (%)	NR	NR	NR	NR
Patients who declined standard therapy, n (%)	NR	NR	NR	NR

Abbreviations: RET: rearranged during transfection; MTC: medullary thyroid cancer; NR: not reported; TC: thyroid cancer.

A2. Priority question. Please provide reasons why there were no standard therapies available for some LIBRETTO-001 trial patients.

As highlighted in response to Clarification Question A1, a series of generic inclusion criteria pertaining to a lack of availability of standard therapies were used to assess eligibility for all patients being enrolled in LIBRETTO-001, regardless of the specific indication; this included the criterion that no standard therapy exists. Based on the LIBRETTO-001 clinical study report (CSR), this criterion most likely applied to patients in cohorts other than the thyroid cancer cohorts, such as those in the tissue agnostic population for which there may not be standard therapies available.

A3. There are four separate categories of patients: (i) cabozantinib/ vandetanib naïve patients with *RET*-mutant MTC, (ii) any line patients with *RET*-mutant MTC, (iii) systemic treatment naïve patients with *RET* fusion-positive TC and (iv) any line patients with *RET* fusion-positive TC. For each of the four categories, please provide the number (and proportion) of patients in the LIBRETTO-001 trial who:

- were from the UK
- continued treatment with selpercatinib after progression.

Patients with *RET*-altered TC and MTC from the UK

The number of patients from the United Kingdom (UK) in the LIBRETTO-001 trial are presented in Table 2, for the cabozantinib/vandetanib naïve (N=143) and any-line MTC patient populations (N=295), and the systemic therapy naïve (N=24) and the any-line TC patient populations (N=65). Overall, [redacted] and [redacted] patients were from the UK in the any-line and cabozantinib/vandetanib naïve MTC patient populations, respectively, while no patients in the TC analysis sets were from the UK. Representation of patients from European countries was greater than representation from the UK, with [redacted]% of patients across the analysis sets from Europe.

Despite having limited patients from the UK, Lilly maintain that the trial populations remain generalisable to the UK. During interviews conducted to support this appraisal, UK clinical experts in thyroid cancer stated that the baseline characteristics of the TC and MTC patient populations were highly representative of UK clinical practice.[1]

Table 2: Patients with *RET*-altered TC and MTC from the UK and Europe in the LIBRETTO-001 trial

Country	*RET*-mutant MTC Cabozantinib/vandetanib naïve N=143	*RET*-mutant MTC Any-line population N=295	*RET* fusion-positive TC Systemic therapy naïve N=24	*RET* fusion positive TC Any-line population N=65
UK	[redacted]	[redacted]	[redacted]	[redacted]
Europe[a]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Countries reported within this category include Denmark, France, Germany, Italy, Spain, Switzerland and the UK.
Abbreviations: MTC: medullary thyroid cancer; NMD: non-measurable disease; RET: rearranged during transfection; TC: thyroid cancer; UK: United Kingdom.

Patients who continued with selpercatinib treatment after progression

The number of patients treated with selpercatinib post-progression was presented in Table 15 and Table 16 of the CS for the *RET*-mutant MTC and RET fusion-positive TC populations, respectively.

For the MTC population, these data were presented for the 'efficacy eligible' MTC population ([redacted]) which captures the any-line (N=295) MTC population in addition to patients with non-measurable disease ([redacted]) (CS, Table 15). However, these data are also available for the any-line MTC population (N=295); [redacted] patients in the any-line MTC populations (N=295) continued with selpercatinib treatment after disease progression.

A4. If AEs were not assessed using the CTCAE criteria, please clarify how they were assessed.

The statement in Table 19, Section B.2.5 of the CS is incorrect; Lilly apologises for this error. As stated in the statistical analysis plan (SAP) for the LIBRETTO-001 trial, each adverse event (AE) was graded based on version 4.03 of the National Cancer Institute common terminology criteria for adverse events (CTCAE).[2] The SAP may be found in the reference pack submitted alongside the original CS.

A5. Please clarify whether the LIBRETTO-001 trial is still recruiting *RET*-mutant MTC patients and *RET* fusion-positive TC patients and, if so, when enrolment is expected to stop.

The LIBRETTO-001 trial is not currently recruiting patients with *RET*-mutant MTC nor *RET* fusion-positive TC.

A6. In the statistical analysis plan (SAP), dated December 2022 (version 3), it is stated (p6) that the rationale for the updated version of the SAP was to define the analysis sets for the final clinical study report. Please provide rationale for all changes made to the efficacy and safety analysis sets since SAP (version 1).

In Section 6.1 of the SAP, dated August 2019 (version 1), three analysis sets were defined for the purpose of an interim analysis.[3] The safety analysis set was defined as all enrolled patients who received at least one dose of selpercatinib. Two additional populations, the dose-limiting toxicity (DTL) analysis set and the patient-reported outcomes (PRO) analysis set, were defined for the purpose of the interim analysis. The SAP (version 1) states that the efficacy analysis will be conducted on the safety analysis set. A PDF version of the SAP (version 1) has been provided in the reference pack alongside this response.[3]

An efficacy analysis set was first defined in the SAP (version 2), dated September 2021, which was used for the Food and Drug Administration (FDA) and European Union (EU) regulatory submissions for selpercatinib.[4] An addendum to the SAP (version 2) was issued for the purpose of defining the necessary analyses for the Japan regulatory submission for the *RET* fusion-positive tissue-agnostic population, specifically.[5] Furthermore, this addendum defined additional analyses based on SAP (version 2). A PDF version of the SAP (version 2) and corresponding addendum have been provided in the reference pack alongside this response.[4, 5]

The definitions of the safety and efficacy analysis sets from Section 3 of the SAP (version 2) are presented in Table 3.

Table 3: Description of safety and efficacy analysis sets as defined in the SAP (version 2)

Participant Analysis Set	Description
Safety analysis set	*RET* fusion-positive cancer patients other than NSCLC and thyroid cancer who were enrolled and received at least one dose of selpercatinib
Efficacy analysis set	*RET* fusion-positive cancer patients other than NSCLC and thyroid cancer who have at least 6 months of follow up from the first dose of selpercatinib at the time of data cutoff. All responders at the time of data cutoff will be followed for at least 6 months from the onset of response unless progressed/died earlier

Abbreviations: NSCLC: non-small cell lung cancer.

The definitions of the analysis sets from Section 3 of the SAP (version 2) Japan addendum are presented in Table 4.

Table 4: Description of analysis sets as defined in the SAP (version 2) Japan addendum

Participant Analysis Set	Description

Safety analysis set	*RET* fusion-positive cancer patients other than NSCLC and thyroid cancer who were enrolled and received at least one dose of selpercatinib
Efficacy analysis set	*RET* fusion-positive cancer patients other than NSCLC and thyroid cancer who have at least 6 months of follow up from the first dose of selpercatinib at the time of data cutoff. All responders at the time of data cutoff will be followed for at least 6 months from the onset of response unless progressed/died earlier
Efficacy analysis set 1 (EAS 1)	Population excluding patients whose starting dose was other than 160 mg BID from the efficacy analysis set
Efficacy analysis set 2 (EAS 2)	Population excluding patients enrolled in cohort 5 from EAS 1
Efficacy analysis set 3 (EAS 3)	Population excluding patients who were determined to have measurable lesions by the investigator but who were determined not to have measurable lesions by IRC assessment from EAS 2
Efficacy analysis set 4 (EAS 4)	Population excluding patients enrolled in cohort 2 from EAS 3
Efficacy analysis set 5 (EAS 5)	Population excluding patients enrolled in the phase 1 part from EAS 4

Abbreviations: EAS: efficacy analysis set; NSCLC: non-small cell lung cancer; IRC: independent review committee.

The purpose of the SAP (version 3), dated December 2022, was to define the analysis sets for the final CSR and detail the statistical methodology to be used to demonstrate the effectiveness and safety of selpercatinib in patients with *RET* advanced solid tumours, including *RET* fusion positive NSCLC and TC, *RET*-mutant positive MTC and other tumours with RET alterations.[2] The description of the safety analysis sets from Section 2.1 of the SAP (version 3) and efficacy analysis sets from Section 2.2 of the SAP (version 3) are presented in Table 5 and Table 6, respectively. A PDF version of the SAP (version 3) has been provided in the reference pack alongside this response.[2]

Table 5: Description of safety analysis sets as defined in the SAP (version 3)

Safety Analysis Set	Analysis Set Description
Overall Safety Analysis Set	All patients who received at least 1 or more doses of selpercatinib regardless of diagnosis or line of therapy
RET fusion-positive NSCLC safety analysis set	All patients with *RET* fusion-positive NSCLC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population
RET-mutant positive MTC safety analysis set	All patients with *RET*-mutant positive MTC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population
RET fusion-positive thyroid safety analysis set	All patients with *RET* fusion-positive thyroid who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population
RET mutant non-MTC safety analysis set[a]	All patients with *RET*-mutant non-MTC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population
Prior RET inhibitor safety analysis set[a]	All patients who have received prior treatment with a selective RET inhibitor. This is a subset of the Overall Safety Population. This group includes patients with *RET* fusion-positive NSCLC, *RET* fusion-positive TC and *RET*-mutant positive MTC

[a] Selected safety analyses will be performed.
Abbreviations: IRC: independent review committee; NSCLC: non-small cell lung cancer; MTC: medullary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.

Table 6: Description of efficacy analysis sets as defined in the SAP (version 3)

Tumour Diagnosis/Line of Therapy	Analysis Set	Analysis Set Description
RET fusion-positive NSCLC	Patients Previously Treated with Platinum-Based Chemotherapy	Efficacy eligible patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy
	Treatment-Naïve Patients	Efficacy eligible treatment-naïve patients with *RET* fusion-positive NSCLC
	Patients Previously Treated with Other Systemic Therapy	Efficacy eligible patients with *RET* fusion-positive NSCLC previously treated with systemic therapies other than platinum-based chemotherapy
	Patients with Non-measurable disease	Efficacy eligible patients with *RET* fusion-positive NSCLC previously treated and treatment-naïve patients without measurable disease by RECIST v1.1
	CNS Response Analysis Set	Efficacy eligible patients with *RET* fusion-positive NSCLC who had investigator-identified CNS metastases at baseline (reported as target or nontarget lesion per RECIST v1.1)
RET mutant-positive MTC	Patients Not Previously Treated with Cabozantinib and/or Vandetanib	Efficacy eligible patients with *RET*-mutant positive MTC that have had no prior systemic therapy or have been treated with a prior systemic therapy besides cabozantinib and vandetanib.
	Patients Previously Treated with Cabozantinib and/or Vandetanib	Efficacy eligible patients with *RET*-mutant positive MTC treated with cabozantinib and/or vandetanib.
	Patients with Non-Measurable Disease	Efficacy eligible patients with *RET*-mutant positive MTC previously treated and treatment naïve patients without measurable disease by RECIST v1.1
	Patients Naïve to Any Systemic Therapy	This analysis set is a subset of the 'Patients Not Previously Treated with Cabozantinib and/or Vandetanib' analysis set
	Patients Naïve to Cabozantinib and Vandetanib But Previously Treated with Other Systemic Therapy	This analysis set is a subset of the 'Patients Not Previously Treated with Cabozantinib and/or Vandetanib' analysis set
RET fusion-positive TC	Patients Not Previously Treated with systemic therapy other than RAI	Efficacy eligible patients with *RET* fusion-positive TC that have had no prior systemic therapy (lenvatinib, sorafenib) other than RAI
	Patients Previously Treated with systemic therapy other than RAI	Efficacy eligible patients with *RET* fusion-positive TC previously treated with systemic therapy (lenvatinib, sorafenib) other than RAI
RET mutant non-MTC[a]	Patients with *RET*-mutant positive non-MTC	Efficacy eligible patients with *RET*-mutant positive non-MTC
Prior *RET* inhibitor[a,b]	Patients who have received prior treatment with a selective RET inhibitor	Efficacy eligible patients with a prior selective RET inhibitor

[a] Selected efficacy analysis will be performed. [b] Group includes patients with *RET* fusion-positive NSCLC, *RET* fusion-positive TC and *RET*-mutant positive MTC, and is excluded from the other efficacy analysis sets.

Abbreviations: CNS: central nervous system; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; RAI: radioactive iodine; RECIST: Response Evaluation Criteria in Solid Tumours; RET: Rearranged during Transfection; SAP: statistical analysis plan; TC: thyroid cancer.

A7. In the CS (Table 8), [redacted] patients in the *RET*-mutant MTC cabozantinib/vandetanib naïve analysis set had received prior systemic therapy; [redacted] patients had received prior systemic therapy with an MKI and [redacted] patients had received "other" prior systemic therapy (summing to a total of [redacted] patients, not [redacted] patients). Please clarify whether [redacted] or [redacted] patients had received prior systemic therapy. If [redacted] patients had received prior systemic therapy, please clarify the types of systemic therapy that the missing nine patients had received.

In total, [redacted] patients in the cabozantinib/vandetanib naïve MTC population had received any prior systemic therapy at baseline. The CS (Document B, Table 8) presented a streamlined information on prior therapies received by patients, focusing on multi-kinase inhibitors (MKIs) and 'Other' therapies.

In addition to these prior therapies, [redacted] patients in the cabozantinib/vandetanib naïve *RET*-mutant MTC population received chemotherapy, while [redacted] of patients received immunotherapy. Table 7 presents these additional treatments, with MKI and 'Other' systemic therapies received by patients also reiterated below for completeness. The sum of all prior systemic therapies is greater than [redacted] patients, as patients could be counted for more than one prior systemic therapy. Further information on prior treatments received by the cabozantinib/vandetanib naïve MTC patient population may be found in Table 14.1.2.3 of the CSR provided in the reference pack alongside the original CS.

Table 7: Prior treatments received by patients with *RET*-mutant MTC

	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Any-line population N=295**
Received prior systemic therapy, n (%)[a]		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Type of prior systemic therapy, n (%)		
Chemotherapy	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
MKI	9 (6.3)	[redacted]
Cabozantinib	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]
Other MKIs	[redacted]	[redacted]
Other	[redacted]	[redacted]
Radioactive iodine	[redacted]	[redacted]
mTOR inhibitor	[redacted]	[redacted]

VEGF/VEGFR inhibitor	[redacted]	[redacted]
Selective *RET* inhibitor	[redacted]	[redacted]
Hormonal therapy	[redacted]	[redacted]
Other systemic therapy	[redacted]	[redacted]

[a] Patients may be counted for more than one systemic therapy, and hence more than one row.
Abbreviations: MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; mTOR: the mammalian target of rapamycin; RET: rearranged during transfection; VEGF: vascular endothelial growth factor; VEGRF: vascular endothelial growth factor receptor.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[6]

A8. In the CS (pp129-130), it is reported that in the LIBRETTO-001 trial, the frequency of reported hypertension AEs by any grade was similar between patients with *RET*-mutant MTC with and without a history of hypertension. Please provide the frequencies for 'Any grade', 'Grade 3' and 'Grade 4' hypertension AEs for:

- patients with *RET*-mutant MTC safety analysis set (SAS) with a history of hypertension
- patients with *RET*-mutant MTC SAS without a history of hypertension
- patients with *RET* fusion-positive TC SAS with a history of hypertension
- patients with *RET* fusion-positive TC SAS without a history of hypertension.

The proportion of patients experiencing any grade, Grade 3 and Grade 4 hypertension adverse events of special interest (AESIs) for the MTC safety analysis set (SAS) and TC SAS are provided below in Table 8, for patients with and without a history of hypertension.

As shown by Table 8, any grade AESIs of hypertension were similar regardless of history of hypertension for the MTC safety analysis set (SAS) ([redacted] of patients with history of hypertension, [redacted] of patients without) and for the TC SAS ([redacted] of patients with history of hypertension, [redacted] of patients without).

As might be expected, rates of Grade 3 hypertension AESIs were elevated for patients with a history of hypertension versus patients without a history of hypertension in the MTC SAS ([redacted] versus [redacted]) and the TC SAS ([redacted] versus [redacted]). However, Grade 4 hypertension AESIs were very rare in all patient populations, with just one Grade 4 AESI recorded across all thyroid cancer analysis sets, occurring in the *RET*-mutant MTC SAS.

Table 8: Hypertension AESIs experienced by patients with and without history of hypertension (MTC and TC SAS)

AE	*RET*-mutant MTC SAS (N=324)		*RET* fusion-positive TC SAS (N=66)	
	With history of hypertension	Without history of hypertension	With history of hypertension	Without history of hypertension
Hypertension				
Any Grade	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]

Grade 4	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Terms 'Hypertension', 'Blood Pressure Abnormal', 'Blood pressure increased' are considered AESI Hypertension. Patients with multiple severity ratings for a given AE are counted under the maximum severity. Patients could also be counted multiple times if several actions were taken.
Abbreviations: AE: adverse event; AESI: adverse event of special interest; MTC: medullary thyroid cancer; RET: rearranged during transfection; SAS: safety analysis set; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[6]

A9. Please provide the frequency of 'withheld doses and dose reductions' for:

- patients with *RET*-mutant MTC SAS with a history of hypertension
- patients with *RET*-mutant MTC SAS without a history of hypertension.

Data on any withheld doses and dose reductions for patients in the *RET*-mutant MTC SAS with and without a history of hypertension are not available. However, data on withheld doses and dose reductions leading to AESIs of hypertension occurring in LIBRETTO-001 for patients with and without a history of hypertension are available; these data are presented in Table 9.

Withheld doses due to hypertension AESIs were uncommon and broadly similar between patients with ([redacted] patients [redacted]) and without ([redacted] patients [redacted]) history of hypertension. Dose reductions were even less common, with [redacted] ([redacted]) patients with and [redacted] ([redacted]) patients without history of hypertension experiencing dose reductions due to a hypertension AESI.

Table 9: Selpercatinib dose modifications resulting from hypertension AESIs for patients with and without a history of hypertension – *RET*-mutant MTC SAS

Dose modification in response to hypertension AESI	*RET*-mutant MTC SAS (N=324)	
	Patients with history of hypertension	Patients without history of hypertension
AESI[a] of hypertension leading to withheld dose	[redacted]	[redacted]
AESI[a] of hypertension leading to dose reduction	[redacted]	[redacted]

[a] Preferred Terms 'Hypertension', 'Blood Pressure Abnormal', 'Blood pressure increased' are considered an AESI of hypertension.
Abbreviations: AESI: adverse event of special interest; MTC: medullary thyroid cancer; RET: rearranged during transfection; SAS: safety analysis set.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[6]

A10. In the CS, Table 21, IRC-assessed DoR rates at ≥60 months are presented for patients with *RET*-mutant MTC. The equivalent data are not presented for investigator-assessed DoR (CS, Appendix N, Table 69). If available, please provide investigator-assessed DoR at ≥60 months.

Investigator assessed rates of duration of response (DOR) were not assessed beyond ≥54 months for patients with *RET*-mutant MTC. Investigator-assessed rates of DOR up to ≥54 months may be found in Table 14.2.3.2 of the CSR provided in the reference pack alongside the original CS.

A11. In the CS (Appendix N, Table 70), investigator-assessed PFS at ≥60 months was presented for patients with *RET*-mutant MTC was presented. The equivalent data are not presented for IRC-assessed PFS (CS, Table 22). If available, please provide PFS at ≥60 months for patients with *RET*-mutant MTC who are cabozantinib/vandetanib naïve and for *RET*-mutant MTC any line patients.

Landmark rates of progression-free survival (PFS) for the cabozantinib/vandetanib naïve MTC patient population and the any-line MTC patient population are provided in Table 10, including the rate of PFS at ≥60 months. All rates of PFS prior to the ≥60-month timepoint were presented in Table 22 of the CS.

At ≥60 months, the rate of PFS for cabozantinib/vandetanib naïve patients with MTC was [redacted] (95% CI: [redacted]), however, rate of PFS was [redacted] for the any-line MTC population (95% CI: [redacted]). The median duration of follow-up in both analysis sets ([redacted]) was substantially shorter than 60 months, therefore, the landmark rate estimate at ≥60 months is associated with uncertainty due to low numbers of patients at risk at this timepoint.

Table 10: Landmark rates of PFS by IRC assessment for patients with *RET*-mutant MTC in the LIBRETTO-001 trial

	***RET*-mutant MTC Cabozantinib/vandetanib naïve N=143**	***RET*-mutant MTC Any-line population N=295**
Rate (%) of PFS		
≥12 months (95% CI)	91.1 (84.8, 94.8)	[redacted]
≥24 months (95% CI)	82.5 (74.8, 88.0)	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
≥60 months (95% CI)	[redacted]	[redacted]
Duration of follow up (months)		
Median (95% CI)	[redacted]	[redacted]

Abbreviation: CI: confidence interval; IRC: independent review committee; MTC: medullary thyroid cancer; PFS: progression free survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[6]

A12. In the CS (Appendix N, Table 72 and Table 73), investigator-assessed DoR and PFS at ≥48 months are presented for patients with *RET* fusion-positive TC. The equivalent data are not presented for IRC-assessed DoR or PFS (CS, Tables 27 and 28, respectively). If available, please provide DoR and PFS at ≥48 months for patients with *RET* fusion-positive TC who are systemic therapy naïve and for *RET* fusion-positive TC any line patients.

Rates of DOR are presented in Table 11 for the systemic therapy naïve and the any-line TC population, including DOR at ≥48 months; all rates of DOR prior to ≥48 months were presented in Table 27 of the CS. Rate of DOR at ≥48 months was [redacted] (95% CI: [redacted]) for the systemic therapy naïve TC population, however, rate of DOR was [redacted] for the any-line TC population

(95% CI: [redacted]). The median durations of follow-up in both analysis sets ([redacted] and [redacted] months for the systemic therapy naïve and any-line TC populations, respectively) are substantially shorter than this timepoint.

Rates of PFS are presented in Table 12 for the systemic therapy naïve and the any-line TC population, including PFS at ≥48 months. All rates of PFS prior to ≥48 months were presented in Table 28 of the CS. Rate of PFS at ≥48 months was [redacted] (95% CI: [redacted]) for the systemic therapy naïve TC population, and rate of PFS was [redacted] for the any-line population (95% CI: [redacted]). The median duration of follow-up in both analysis sets ([redacted] and [redacted] months for the systemic therapy naïve and any-line TC populations, respectively) are shorter than this timepoint.

Due to the length of follow-up in these patient populations, estimates for DOR and PFS at ≥48 months are associated with some uncertainty due to low numbers of patients at risk.

Table 11: Landmark rates of DOR by IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC Systemic therapy naïve N=24**	***RET* fusion-positive TC Any-line Population N=65**
Rate (%) of DOR		
≥12 months (95% CI)	100.0 (NE, NE)	[redacted]
≥24 months (95% CI)	90.9 (50.8, 98.7)	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
Duration of follow up (months)		
Median (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; IRC: independent review committee; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[6]

Table 12: Landmark rates of PFS by IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC Systemic therapy naïve N=24**	***RET* fusion-positive TC Any-line population N=65**
Rate (%) of PFS		
≥12 months (95% CI)	95.2 (70.7, 99.3)	[redacted]
≥24 months (95% CI)	95.2 (70.7, 99.3)	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
Duration of follow up (months)		
Median (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IRC: independent review committee; PFS: progression free survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[6]

LIBRETTO-531

A13. Please provide the results of proportional hazards assessments (i.e., Schoenfeld residuals plots and tests) for progression-free survival (PFS), overall survival (OS) and duration of response (DoR) for the LIBRETTO-531 trial.

A summary of the proportional hazards tests for the LIBRETTO-531 trial are presented below.

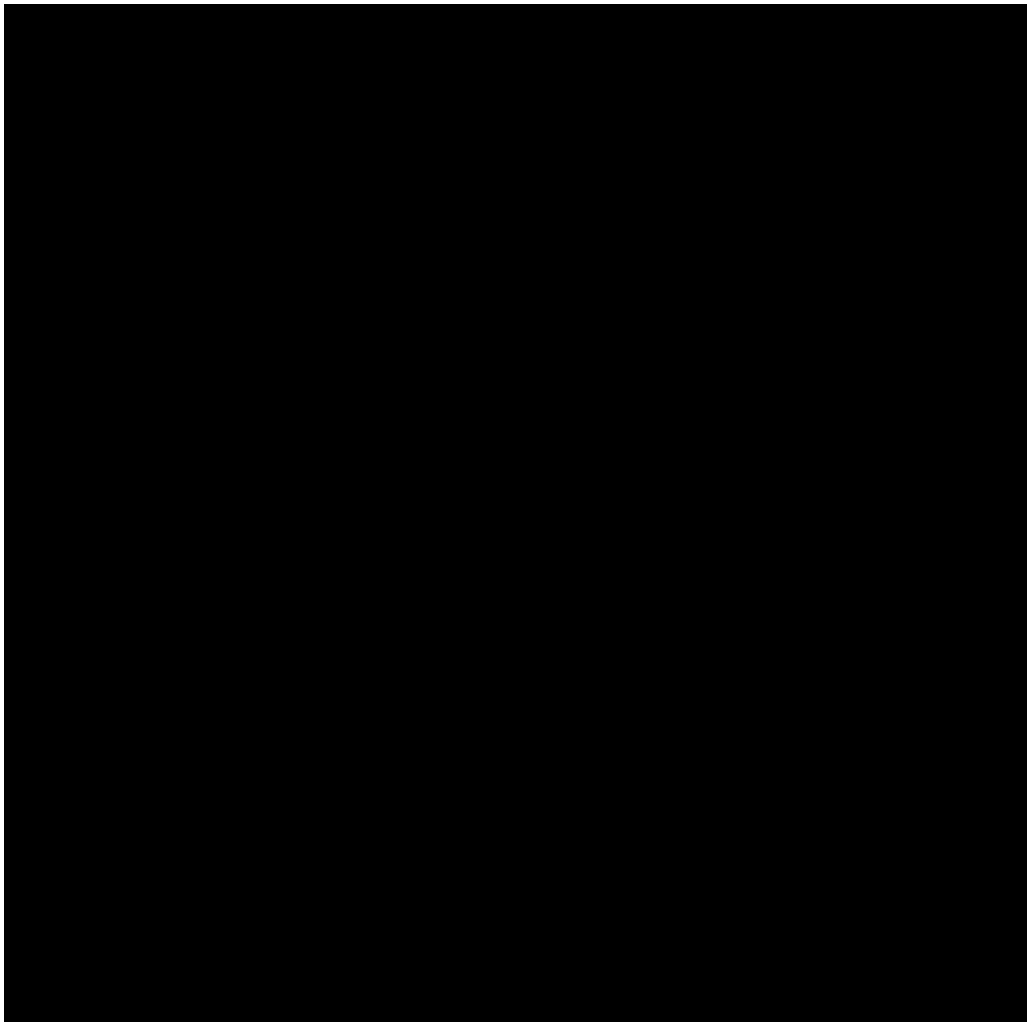
The results of the global Schoenfeld test are presented in Table 13, and Schoenfeld residuals plots for PFS, overall survival (OS) and DOR are presented in Figure 1 to Figure 3. Based on inspection of the Schoenfeld residual plots and the global Schoenfeld residuals test of proportional hazards, the proportional hazard assumption appears to hold for OS, PFS and DOR, based on the p-values >0.05 and the relatively flat nature of the Schoenfeld residual curves.

Table 13: Global Schoenfeld residuals test of proportional hazards for selpercatinib versus cabozantinib/vandetanib (LIBRETTO-531)

Comparison	p-value
OS	[redacted]
PFS (BICR)	[redacted]
DOR (BICR)	[redacted]

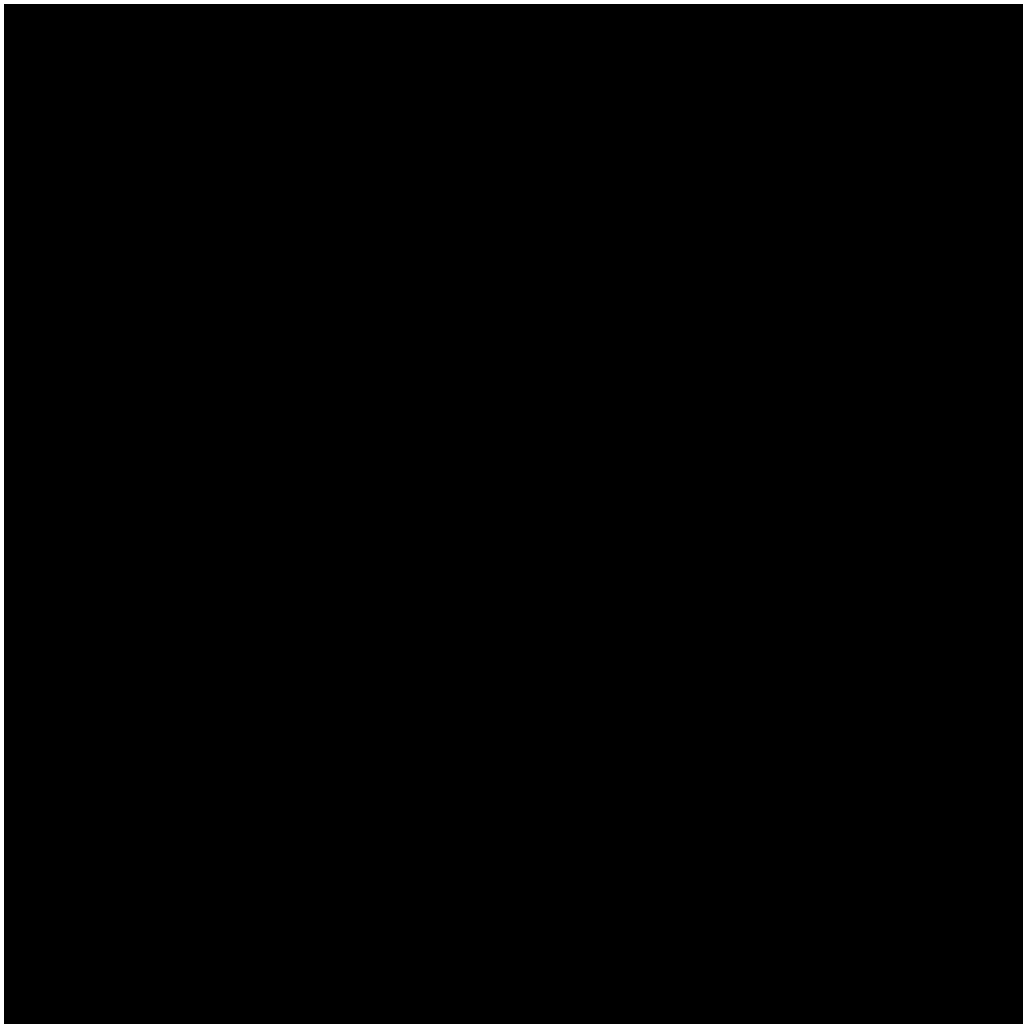
Abbreviations: BICR: Blinded independent committee review; DOR: duration of response; OS: overall survival; PFS: progression free survival.

Figure 1: Schoenfeld residual plot for OS for selpercatinib versus cabozantinib/vandetanib (LIBRETTO-531)



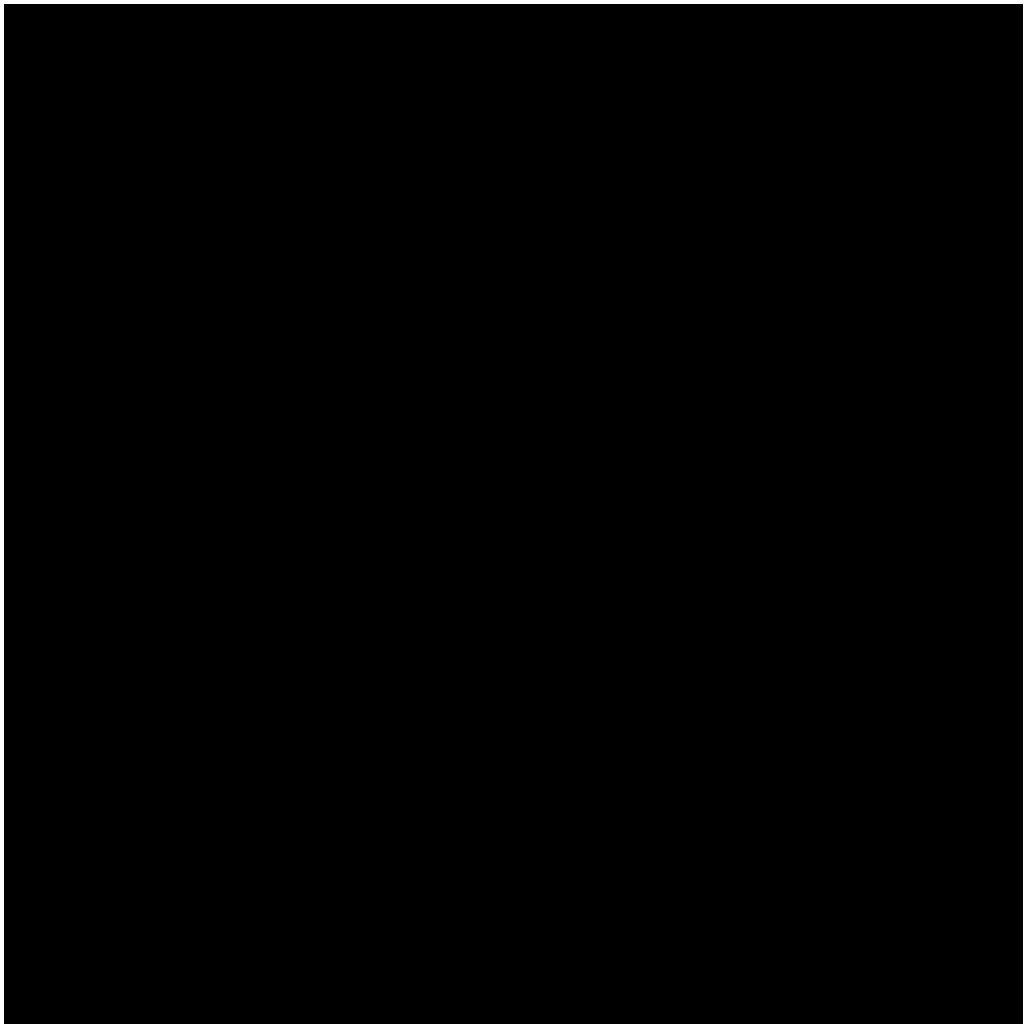
Abbreviations: OS: overall survival.

Figure 2: Schoenfeld residual plot for PFS (BICR) for selpercatinib versus cabozantinib/vandetanib (LIBRETTO-531)



Abbreviations: BICR: Blinded independent committee review; PFS: progression free survival.

Figure 3: Schoenfeld residual plot for DOR (BICR) for selpercatinib versus cabozantinib/vandetanib (LIBRETTO-531)



Abbreviations: BICR: Blinded independent committee review; DOR: duration of response.

A14. Please provide the hazard ratios (HRs) and medians (95% confidence intervals [CIs]) for PFS and OS, and the odds ratio (OR) and number (and proportion) of LIBRETTO-531 patients for overall response rate (ORR) for the comparison of selpercatinib (N=193) versus cabozantinib only (N=73).

Comparisons of selpercatinib versus cabozantinib from LIBRETTO-531, in terms of PFS, OS and ORR, are available for the selpercatinib ([redacted]) and cabozantinib ([redacted]) populations. Comparison of selpercatinib versus cabozantinib are available from the 22nd May 2023 data cut-off and are presented in Table 14. The selpercatinib and cabozantinib populations are smaller than the efficacy and safety data presented in the CS (Section B.2.6.3 and B.2.10.5), featuring N=193 patients receiving selpercatinib and N=73 patients receiving cabozantinib, as these analysis sets only included patients for whom cabozantinib was a treatment option.

As shown by Table 14, median PFS was [redacted] for selpercatinib (95% CI: [redacted]) while median PFS for cabozantinib was [redacted] (95% CI: [redacted]). The hazard ratio (HR) for selpercatinib versus cabozantinib was [redacted] (95% CI: [redacted]) indicating that selpercatinib decreased the risk of disease progression by [redacted] compared with cabozantinib.

Similarly, median OS was [redacted] in the selpercatinib population (95% CI: [redacted]), however, median OS was [redacted] months (95% CI: [redacted], [redacted]) in the cabozantinib population. The resulting OS HR was [redacted] ([redacted]) for selpercatinib versus cabozantinib, indicating that selpercatinib decreases the risk of death by [redacted] compared with cabozantinib. When interpreting the OS results, the fact that cabozantinib patients were permitted to cross-over to the selpercatinib arm following disease progression should be considered.[7]

The ORRs for the selpercatinib and cabozantinib populations were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. The corresponding odds ratio (OR) for ORR was [redacted] (95% CI: [redacted]) for selpercatinib versus cabozantinib, indicating the high comparative rate of response for patients receiving treatment with selpercatinib.

Overall, initial results from LIBRETTO-531 demonstrate a clinically meaningful benefit in terms of PFS, OS and ORR, supporting the conclusions of the indirect treatment comparisons (ITCs) for the *RET*-mutant MTC patient population in the CS.

Table 14: PFS (BICR), OS and ORR (BICR) for selpercatinib versus cabozantinib (LIBRETTO-531 trial; 22nd May 2023 DCO)

	Selpercatinib [redacted]	Cabozantinib [redacted]
PFS		
Median, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
OS		
Median, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
ORR		
ORR (%)	[redacted]	[redacted]
OR	[redacted]	

Abbreviations: BICR: blinded independent committee review; CI: confidence interval; DCO: data cut-off; HR: hazard ratio; OR: odds ratio; ORR: overall response rate; OS: overall survival; PFS: progression free survival.

A15. Please provide LIBRETTO-531 trial HRQoL results (i.e., EORTC QLQ-C30).

Health-related quality of life (HRQoL) data are not yet available from LIBRETTO-531. These data are expected to become available in [redacted].

A16. Please provide a quality assessment of the LIBRETTO-531 trial using the seven question checklist based on the recommendations of the Centre for Reviews and Dissemination.

A quality assessment of the LIBRETTO-531 trial, using the seven-question checklist based on the Centre for Reviews and Dissemination, has been conducted and the results of this quality assessment are presented in Table 15. Due to the late-breaking nature of the LIBRETTO-531 trial and the current unavailability of a CSR, the quality assessment has been conducted based on the LIBRETTO-531 publications only.

Overall, the LIBRETTO-531 trial was considered a high-quality trial, with a robust design and largely balanced treatment arms. The differences in dropouts and treatment continuations

between the treatment arms may be expected due to the improved efficacy and tolerability of selpercatinib versus comparators (cabozantinib and vandetanib).

Table 15: Quality assessment of the LIBRETTO-531 trial

Trial name	**LIBRETTO-531 (NCT04211337)[8]**	
Reference	Hadoux, J., Elisei, R., Brose, M.S., Hoff, A.O., Robinson, B.G., Gao, M., Jarzab, B., Isaev, P., Kopeckova, K., Wadsley, J. and Führer, D., 2023. Phase 3 trial of selpercatinib in advanced *RET*-mutant medullary thyroid cancer. New England Journal of Medicine.[9]	
Criteria for assessment of risk of bias in RCTs	**(Yes/no/unclear/ NA)**	**Comment**
Was randomisation carried out appropriately?	Yes	Eligible patients were allocated to two arms in a 2:1 ratio to receive selpercatinib or control (cabozantinib or vandetanib), respectively.
Was the concealment of treatment allocation adequate?	No	This was an open-label study between selpercatinib and physician's choice (cabozantinib/vandetanib). However, the sponsor was blinded to the aggregate data (i.e., did not review or analyse data).
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	The treatment arms are well balanced except for the gender difference. Regarding the difference in median time from diagnosis to baseline, the confidence intervals are very wide. It is unclear as to whether this is a meaningful difference. • The relative indolent nature of MTC with large variations in records of time of diagnosis could be the reason for the above. Eligibility criteria for LIBRETTO-531 included progressive disease within 14 months of baseline, confirmed by BICR.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No	This was an open-label study; hence, allocations were not masked from the patient or the investigator. However, the outcomes were assessed by BICR.
Were there any unexpected imbalances in dropouts between groups?	Yes	Proportions of dropouts (Protocol deviations, withdrawal by patients, patients who did not receive treatment): • The patient dropouts were higher in the control arm (9.1% [9/98]) when compared to the selpercatinib arm (2.5% [5/193]). Proportions of total treatment discontinuations: • All-cause discontinuations were higher in the control arm (58% [57/98]) when compared to the selpercatinib arm (9.3% [18/193]).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The authors reported the efficacy and safety endpoints that were described in the methods section.
Did the analysis include an intention-to-treat (ITT) analysis? If	Yes	ITT analysis was performed. All members of both the arms were included and analysed as part of the group they were assigned to. None of the patients

so, was this appropriate, and were appropriate methods used to account for missing data?		took wrong medication, all were treated with the assigned therapy in both arms. The data for dropouts and reasons were also mentioned in the CONSORT diagram.

Abbreviations: BICR: blinded independent committee review; CONOSRT: Consolidated Standards of Reporting Trials; ITT: intention-to-treat; MTC: medullary thyroid cancer; NA: not applicable; RTC: randomised control trial;

ITCs

A17. In the CS, p104, it is stated that *'sex and smoking status were not identified as prognostic factors for MTC in the SLR, which was confirmed by prior clinical expert feedback obtained during the NICE appraisal TA742'*. Please clarify why sex and smoking status were included in the list of variables adjusted for in the MAIC (CS, p105).

As stated above, smoking status and sex were not identified as prognostic in the SLR conducted to identify prognostic factors relevant to MTC. However, the variables that were adjusted for in the MAICs were identified in line with guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, considering evidence from the SLR, clinical expert opinion gathered to support this appraisal and prior opinion gathered to support TA742. During clinical expert interviews conducted to support this appraisal, UK clinical experts confirmed that sex and smoking status are prognostic factors and it was therefore appropriate for them to be adjusted for in the MAICs.

Clinical expert feedback obtained during an interview conducted in 2020 as part of NICE TA742 highlighted that sex and smoking status were not prognostic for thyroid cancer *specifically*.[10, 11] However, evidence from the published literature supports the inclusion of sex and smoking status as prognostic factors for survival more generally. The published literature has previously identified sex disparities in thyroid cancer, with a 2021 Surveillance, Epidemiology, and End Results (SEER) population study investigating 41,270 females and 13,188 males with thyroid cancer finding that sex was prognostic factor for OS and cancer-specific survival (CSS).[12] When considering subgroup analyses in the LIBRETTO-001 trial, a numerical difference in response rate was also identified for males and females; ORR was [redacted] in males and [redacted] Therefore, an imbalance in sex between trials is likely to have an impact on overall survival observed for the two populations. In addition, smoking status is recognised as a prognostic factor for overall survival in the general population, thus, an imbalance in smoking status between trials can be expected to have an impact on the overall survival of the cohorts, irrespective of the impact on cancer-specific survival.[13]

As outlined in NICE DSU TSD 18, weighting methods for unanchored indirect comparisons should adjust for all effect modifiers and prognostic variables in order to reliably predict absolute outcomes.[14] As such, smoking status and sex were adjusted for in the unanchored MAIC analysis, and this approach is in line with the approach accepted by the Committee in NICE TA742. After weighting, the sample size of the LIBRETTO-001 any-line MTC population (N=295) remained sufficiently large after matching (Neff=[redacted]) to produce robust comparative efficacy estimates.

Patients aged 12 to 18 years

A18. Please clarify if there is any clinical efficacy and/or safety evidence available specifically for patients aged 12 to 18 years who were treated with selpercatinib? If so, please provide a brief summary of the evidence.

The LIBRETTO-001 trial represents the pivotal clinical trial for selpercatinib, as the first in-human Phase I/II study enrolling patients with advanced, *RET*-altered solid tumours. The LIBRETTO-001 trial recruited patients ≥12 years of age. As was shown in Table 7 and Table 9 in the CS, the minimum baseline age of both the cabozantinib/vandetanib naïve and any-line MTC patient populations was 15. Specifically, [redacted] was present in the cabozantinib/vandetanib naïve MTC population ([redacted] years old at consent to participate) and [redacted] adolescent patients were present in the any-line MTC population (ages [redacted], [redacted] and [redacted] years at consent to participate). However, minimum age in the TC patient populations was 20 years of age, thus, no adolescent patients were included in these populations.

Incidence rates for thyroid cancer are highest between the ages of 65 to 69 years.[15] Combined with the rarity of advanced thyroid cancer cases, there are a low number of cases of advanced, *RET*-altered TC and MTC in adolescent patients, making recruitment of these patients into trials challenging.

Section B: Clarification on cost effectiveness data

B1. Priority question. Data provided in the CS (Table 65) show wide discrepancies between clinical expert and company model 10-year and 20-year OS estimates for patients with *RET*-mutant MTC treated with selpercatinib. Please provide cost effectiveness results generated using an OS curve for the *RET*-mutant MTC population treated with selpercatinib that produces 10-year and 20-year survival estimates that align with clinical advice provided to the company.

As outlined in the CS (Section B.3.3.3), the base case extrapolations were selected per the recommendations provided in NICE DSU TSD14, including consideration of the goodness-of-fit of the models to the trial data and considering of short-term and long-term clinical plausibility.[16] For the OS extrapolation in the *RET*-mutant MTC population, the stratified Weibull extrapolation was selected for all treatments; as the most pessimistic OS curve for selpercatinib, the stratified Weibull aligned most closely with the estimates provided by the UK clinical experts

Whilst Lilly maintain that the stratified Weibull represents the most appropriate of the explored extrapolations, Lilly acknowledge that the OS for selpercatinib based on the stratified Weibull curve is overestimated versus the estimates provided by UK clinical experts. As such, the base case has been updated to include an adjustment factor applied to the selpercatinib OS curve in the *RET*-mutant MTC population from five years onwards to generate an OS curve that is more closely aligned with the estimates provided by the UK clinical experts at 10 and 20 years, as presented in Table 16. Once the 1.0 adjustment factor is applied, 10-year and 20-year survival

estimates for patients with *RET*-mutant MTC treated with selpercatinib lie in the range predicted by UK clinical experts in thyroid cancer, ([redacted]% and [redacted]%, respectively).

The revised cost-effectiveness model constructs survival functions by applying a user-adjustable multiplying factor. The adjustment factor is applied to the OS hazard rate in the model to reconstruct survival functions, calculated from the original parametric model based on survival probabilities. Modified survival probabilities then reduce the overestimation of OS in the updated OS curve for selpercatinib. In the updated base case for the *RET*-mutant MTC population, the adjustment factor is set to 2.0 and is applied from five years onwards, but this is user-adjustable in the model ('Survival – MTC' sheet, D71:D76). Further information on the application of the adjustment factor in the model are provided in Appendix B.

Results of the updated base case cost-effectiveness analysis, including the revised extrapolation of selpercatinib OS, are presented in Appendix A.

Table 16: Comparisons of selpercatinib OS for *RET*-mutant MTC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	[redacted]	[redacted]	[redacted]
Original company base case				
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case				
Stratified Weibull (2.0 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; NA: not applicable; OS: overall survival; RET: rearranged during transfection.
Source: Lilly Data on File. Clinical Validation Meeting Minutes. 2023.[1]

B2. Priority question. Data provided in the CS (Table 70) show wide discrepancies between clinical expert and company model 10-year and 20-year OS estimates for patients with *RET* fusion-positive TC treated with selpercatinib. Please provide cost effectiveness results generated using an OS curve for the *RET* fusion-positive TC population treated with selpercatinib that produces 10-year and 20-year survival estimates that align with clinical advice provided to the company.

As highlighted in response to Clarification Question B1, the base case extrapolations were carefully selected in line with NICE DSU TSD14, including the consideration of the clinical plausibility of long-term estimates. For OS in the RET fusion-positive TC population, the piecewise exponential model was selected to model OS for all treatments (Section B.3.3.4). Considering the UK clinical expert estimates that approximately 35–50% and 5–15% of patients would be alive at 10 and 20 years, respectively, the OS estimates provided by the piecewise exponential model are broadly aligned, with [redacted] and [redacted] of patients in the selpercatinib arm estimated to be alive at 10 and 20 years, respectively. In fact, the estimate provided by the piecewise exponential model at 10 years slightly underestimates survival for selpercatinib based on the UK clinical expert estimates.

Regardless, for consistency with the approach adopted in response to Clarification Question B1, the base case has been updated to apply an adjustment factor to the selpercatinib OS curve in the *RET*-fusion positive TC population to generate OS estimates that are aligned with the estimates from UK clinical experts, as presented in Table 17.

The adjustment factor was applied in the same was as described in response to Clarification Question B1. However, in the revised company base case for the *RET* fusion-positive TC population, this adjustment factor was set to 1.2 as a smaller adjustment was required to align the estimates with those provided by the UK clinical experts. This input is user-adjustable in the model ('Survival – TC' sheet, D57:D62').

Results of the updated base case cost-effectiveness analysis are presented in Appendix A.

Table 17: Comparisons of selpercatinib OS for *RET* fusion-positive TC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	[redacted]	[redacted]	[redacted]
Original company base case				
Piecewise exponential	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case				
Piecewise exponential (1.2 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA: not applicable; OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Lilly Data on File. Clinical Validation Meeting Minutes. 2023.[1]

B3. Priority question. Please provide a company model that allows relative dose intensity to be applied directly to all treatments from the first model cycle.

As outlined in the CS (Section B.3.5.1), no dose reductions are applied for selpercatinib or comparators in the first treatment cycle, however relative dose intensity for selpercatinib and comparators was applied for subsequent cycles in the model.

Although Lilly acknowledge that a dose intensity lower than 100% may be used in UK clinical practice for both selpercatinib and the comparators, this is anticipated to have minimal impact on the ICER. For selpercatinib, assuming a 100% dose intensity in the first cycle represents a conservative assumption. For the comparators, several conservative assumptions to reduce the costs associated with cabozantinib and lenvatinib, such as no drug wastage (i.e., pack sharing), have already been incorporated in the base case. As such, the model has not been revised to include this amendment.

B4. Priority question. Please provide a company model that follows patients until ≤1% of patients are alive in each treatment arm.

As highlighted in the CS (Section B.3.2.2), a time horizon of 25 years was used in the base case to represent a lifetime horizon. This aligned was with previous NICE appraisals in advanced thyroid cancer.[10, 17]

However, in response to the request from the EAG, the time horizon of the model has been extended to 35 years, which results in less than 2% of patients in each treatment arm being alive at the end of the model time horizon. This assumption has been updated in the updated base case cost-effectiveness analysis. Results of the updated base case cost-effectiveness analysis are presented in Appendix A.

B5. Priority question. In the company *RET*-mutant MTC model, patients treated with selpercatinib live an average of [redacted] years in the progressed disease health state whereas patients treated with cabozantinib live an average of [redacted] years in the progressed disease health state.

In the company TC model, patients treated with selpercatinib live an average of [redacted] years in the progressed disease health state whereas patients treated with lenvatinib, sorafenib and BSC live an average of [redacted] years, [redacted] years and [redacted] years, respectively, in the progressed disease health state.

Please provide evidence to support:

- **patients living for many years in the progressed disease health state despite no active therapies and a utility value of 0.5, suggesting a substantial symptom burden**
- **the substantial differences in time alive in the progressed disease health state depending on the active treatment received whilst in the progression-free health state.**

In response to Clarification Questions B1 and B2, Lilly have applied an adjustment to the OS curve for selpercatinib such that the long-term OS estimates more closely align with the UK clinical expert estimates. The time spent by patients in each treatment arm in the progressed disease (PD) health state based on the revised base case analysis is therefore reduced when compared to the original company base case.

Patients living in the PD health state for many years

Lilly acknowledge that no active treatments are available for patients following progression on their first-line treatment, however, the disease course of thyroid cancer can allow patients to live for many years following progression of their disease, albeit with a reduced HRQoL.

This conclusion was also supported by estimates of the proportion of selpercatinib patients alive and progression-free at landmark timepoints provided by UK clinical experts. Specifically in the *RET*-mutant MTC population, UK clinical experts estimated that 25–30% of patients receiving selpercatinib would be alive at 15 years, with 10–12.5% of patients progression-free at the same timepoint, demonstrating that a proportion of patients that are alive would also have progressed disease.[1] When comparing the OS estimates at 15 years with the PFS estimates at earlier timepoints, such as 10 years, it is apparent that the UK clinical expert estimates support the potential for patients to live for a period of time following disease progression. At 10 years, 20–

25% of patients are estimated to be progression-free whilst 25–30% of patients are estimated to be alive at 15 years.[1] As the OS estimate at 15 years is higher than the PFS estimate at 10 years, a proportion of patients (approximately 5% based on the above estimates) alive at 15 years are assumed to have already progressed at 10 years.

This is further supported by the published literature. In particular, a real-world study conducted in Germany demonstrated a median OS for patients receiving vandetanib of 53 months, while the median PFS was just 17 months, reflecting 36 months living with progressed disease.[18] Furthermore, in patients with bone metastases at the time of initiation of treatment with vandetanib, median OS was 52 months and median PFS was 17 months, thereby demonstrating that patients with thyroid cancer have the potential to live for a substantial period of time with progressed disease.[18]

Difference in time spent in the PD health state between treatment arms

In terms of the difference in time spent in the PD health state between treatment arms, following the updates to the base case outlined in response to Clarification Questions B1 and B2, the difference in time spent in the PD health state between treatment arms is decreased. As highlighted in the CS (Section B.3.3.5), patients receiving selpercatinib in the model are assumed to remain on treatment for [redacted] weeks and [redacted] weeks following disease progression for patients with *RET*-mutant MTC and *RET* fusion-positive TC, respectively. In contrast, patients receiving the comparator treatments are assumed to stop treatment immediately following progression.

These assumptions were based on feedback from UK clinical experts who stated that patients would typically remain on treatment with selpercatinib for a period of time following progression due to the symptomatic benefits. In contrast, due to the toxicity profile of currently available MKIs, patients are likely to discontinue treatment sooner following progression. As such, it is expected that patients receiving selpercatinib would continue to receive some survival benefits following discontinuation when compared with the comparator treatments. Moreover, due to the toxicity profile of currently available MKIs, patients are likely to be less fit when their disease progresses, compared with patients experiencing progression of their disease on selpercatinib. As such, it is expected that patients receiving MKIs may live for a shorter period of time following progression of their disease than patients receiving selpercatinib.

The potential for patients to experience differences in times alive following disease progression is also supported by the aforementioned real-world evidence study.[18] Based on this study, for patients receiving vandetanib, median PFS was 17 months and median OS was 53 months; for patients receiving cabozantinib, median PFS was 4 months and median OS was 24 months. This demonstrates a difference between median PFS and median OS of 36 months for patients receiving vandetanib compared with 20 months for patients receiving cabozantinib, thereby supporting the potential for patients to live for different durations of time following disease progression depending on the active treatment received.

As such, Lilly maintain that the estimates produced by the cost-effectiveness model are clinically plausible. Furthermore, this represents an inevitable limitation of the partitioned survival approach due to OS and PFS being independently extrapolated, leaving the potential for large differences in the proportion of patients in the OS and PFS curves at specific timepoints.

Regardless, for the *RET*-mutant MTC population, only [redacted]% of total QALYs for selpercatinib are accrued in the PD health state, with the remaining [redacted]% being accrued in the PFS health state; the corresponding values for the *RET* fusion-positive TC population are [redacted]% and [redacted]%. As

such, although patients may spend an extended period of time in the PD health state, around three quarters of the QALYs for selpercatinib are accumulated in the PFS health state. Considering incremental QALY gains in the *RET*-mutant MTC population, for selpercatinib versus cabozantinib and selpercatinib versus BSC, [redacted]% and [redacted]% of incremental QALYs are accrued in the PD health state, respectively; in the *RET* fusion-positive TC population, [redacted]% and [redacted]% of incremental QALYs for selpercatinib versus lenvatinib and selpercatinib versus BSC are accrued in PD health state, respectively. This should therefore not be considered a substantial source of uncertainty.

Section C: Textual clarification and additional points

C1. Please provide the clinical study report (CSR) for the LIBRETTO-531 trial.

No CSR for the LIBRETTO-531 trial is available at this time. A CSR is anticipated to become available in [redacted].

C2. The URL link provided for the Summary of Product Characteristics (SmPC) for Retsevmo 40mg hard capsule (CS, reference number 1) does not work. Please provide the correct URL link and/or the PDF version of the SmPC.

The Summary of Product Characteristics (SmPC) for Retsevmo 40mg hard capsule can be accessed via MHRA Products | Search Results upon reviewing and accepting the disclaimer.[19] A PDF version of the SmPC has also been provided in the reference pack alongside this response.

C3. In the CS, Table 6, it is stated that the first LIBRETTO-001 trial patient was "treated on 9th May 2017". Please clarify whether this refers to the initiation date of phase I or phase II of the LIBRETTO-001 trial.

The first patient in the LIBRETTO-001 trial was treated on 9th May 2017, which corresponds to the initiation of Phase I of the LIBRETTO-001 trial.

C4. It is stated in the CS that "*the large discrepancy in PFS and OS HRs for cabozantinib versus placebo are likely due to the permitting of cross-over from the placebo arm to the cabozantinib arm in the EXAM trial"* (CS, p162). However, it is stated in the EXAM trial publication (Schlumberger et al 2017) that patients in the placebo arm were not permitted to crossover to cabozantinib. If possible, please provide an alternative explanation for the large discrepancy in PFS and OS HRs for the comparison of cabozantinib versus placebo.

Lilly would like to clarify that the statement on page 162 of the CS is an error. The large discrepancy in PFS and OS HRs for cabozantinib versus placebo is instead likely due to a higher proportion of patients in the placebo arm (49.5% [55/111]) receiving subsequent systemic therapies compared with the cabozantinib arm (31.5% [69/219]) in the EXAM trial. Of these therapies, 26.9% (59/219) patients in the cabozantinib arm received tyrosine kinase inhibitors (TKIs), compared to 41.4% (46/111) in the placebo arm. The heavy treatment of patients with subsequent anticancer therapies in both trial arms is anticipated to confound OS results in the

EXAM trial, as acknowledged by the committee in NICE TA516, although the extent of this effect is not known.[20]

This is supported by conclusions in Schlumberger, *et al.* 2017 publication stating that there was no OS benefit observed with cabozantinib versus placebo in the patient population receiving subsequent therapy (HR, 0.93; 95% CI, 0.63–1.39), while cabozantinib demonstrated an OS benefit in patients who did not receive subsequent therapy (HR, 0.59; 95% CI, 0.39–0.88).[21]

C5. Please update CS, Table 1 to include the rows titled 'Economic analysis' and 'Other considerations', as per the final scope issued by NICE.

Table 18 of the CS has been updated below to include the rows titled 'Economic analysis' and 'Other considerations'. No changes have been made to the rows originally included in the CS. As shown, there are no substantial deviations from the final scope issued by NICE.

Table 18: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Populations	***RET*-fusion positive TC:** Adults with untreated advanced *RET*-fusion positive thyroid cancer who require systemic therapy ***RET*-mutant MTC:** Adults and adolescents 12 years and older with untreated advanced *RET*-mutant MTC who require systemic therapy	***RET*-fusion positive TC:** Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy) ***RET*-mutant MTC:** Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)	***RET*-fusion positive TC:** NA – in line with the NICE final scope ***RET*-mutant MTC:** NA – in line with the NICE final scope
Intervention	Selpercatinib	Selpercatinib	NA – in line with the NICE final scope
Comparator(s)	***RET* fusion-positive TC:** • Lenvatinib • Sorafenib • Best supportive care (BSC) ***RET*-mutant MTC:** • Cabozantinib (adults only) • BSC	***RET*-fusion positive TC:** • Lenvatinib • BSC ***RET*-mutant MTC:** • Cabozantinib • BSC	***RET*-fusion positive TC:** In this submission, lenvatinib is positioned as the primary comparator in the TC indication, of most relevance to decision making. Clinical expert opinion obtained to support the development of this submission confirmed that lenvatinib is the predominant MKI used in UK clinical practice, due to a perceived improved efficacy and similar adverse event profile with respect to sorafenib.[1] UK clinical experts indicated for patients receiving MKIs, the vast majority (90%-95%) of patients receive lenvatinib.[1] UK clinical experts stated that

			sorafenib is rarely used, when compared with lenvatinib, so sorafenib is not considered a relevant comparator in this appraisal. BSC is positioned as secondary comparators in this submission. BSC is only received by patients ineligible for treatment with an MKI, including children and adolescents aged 12–17 years. Clinical expert opinion indicates that 90–95% of patients in the TC indication would receive a MKI.[1] ***RET*-mutant MTC:** In line with the NICE final scope. In this submission, cabozantinib is positioned as the primary comparator in the MTC indication. Clinical expert opinion gained to validate the MTC treatment pathway in the UK estimated that 85–95% of individuals with advanced *RET*-mutant MTC in the UK will receive treatment with cabozantinib.[1] BSC is positioned as a secondary comparator in this submission in the MTC indication. BSC is only received by patients who are ineligible for treatment with cabozantinib, including patients who may be unable to tolerate the associated toxicity profile and children and adolescents aged 12–17 years.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rate • Adverse effects (AEs) of treatment • Health-related quality of life	**Primary endpoints** • Best overall response (BOR) and objective response rate (ORR) **Key secondary endpoints** • Duration of response (DOR) • Time to response and time to	NA – in line with the NICE final scope

	(HRQoL)	best response • Clinical benefit rate (CBR) • OS • PFS • AEs • HRQoL	
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 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 or fusion in people with advanced MTC/advanced thyroid cancer who would not otherwise have been tested.	The economic analysis has been provided in line with the NICE reference case **Outcomes:** As per page 141 of Document B, the ICER of selpercatinib versus each comparator was evaluated in terms of an incremental cost per QALY gained **Model time horizon:** 25 years in base case **Model perspective:** As per page 139 of Document B, the analysis was conducted from the perspective of the NHS and Personal Social Services. **Commercial arrangements:** A confidential Patient Access Scheme of [redacted]% has been provided alongside this submission. The commercial arrangements for comparators in this submission are not known **Diagnostic testing for *RET* fusions:** The cost of *RET* testing has been included in the base case of the economic model, in line with TA911.[22]	The model base case is in line with the NICE final scope. No scenario analyses for *RET* testing were conducted, as excluding costs of *RET* testing is anticipated to have minimal impact on cost-effectiveness results.

	A sensitivity analysis should be provided without the cost of the diagnostic test	Exclusion of *RET* testing was not considered as a scenario analysis	
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	NA	NA – in line with the NICE final scope

Abbreviations: AE: adverse event; BOR: best overall response; BSC: best supportive care; CBR: clinical benefit rate; DOR: duration of response; HRQoL: health-related quality of life; ICER: Incremental cost-effectiveness ratio; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; NA: not applicable; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; ORR: objective response rate; OS: overall survival; PFS: progression free survival; QALY: Quality-adjusted life year; *RET*: rearranged during transfection; TC: thyroid cancer; UK: United Kingdom.

Appendix A: Revised base case cost-effectiveness analysis

As detailed throughout the responses above, some assumptions have been updated in the base case economic analyses in response to the requests from the EAG. An overview of the updated assumptions is presented in Table 19 and Table 20 for the *RET*-mutant MTC and *RET* fusion-positive TC populations, respectively.

Table 19: Assumptions updated in the base case and associated incremental ICER for the *RET*-mutant MTC population (deterministic – selpercatinib PAS price)

Submitted base case assumption	Updated base case assumption (related Clarification Question)	ICER incremental (£/QALY)
Original base case: selpercatinib versus cabozantinib		29,560
Stratified Weibull selected to model OS for all treatments	Stratified Weibull selected to model OS for all treatments with an adjustment applied to the selpercatinib OS to more closely align with UK clinical expert estimates (Clarification Question B1)	35,255
25-year time horizon	35-year time horizon (Clarification Question B4)	28,865
Updated base case: selpercatinib versus cabozantinib		**35,656**
Original base case: selpercatinib versus BSC		40,219
Stratified Weibull selected to model OS for all treatments	Stratified Weibull selected to model OS for all treatments with an adjustment applied to the selpercatinib OS to more closely align with UK clinical expert estimates (Clarification Question B1)	47,256
25-year time horizon	35-year time horizon (Clarification Question B4)	39,054
Updated base case: selpercatinib versus BSC		**47,377**

Abbreviations: ICER: incremental cost-effectiveness ratio; MTC: medullary thyroid cancer; OS: overall survival; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

Table 20: Assumptions updated in the base case and associated incremental ICER for the *RET* fusion-positive TC population (deterministic – selpercatinib PAS price)

Submitted base case assumption	Updated base case assumption (related Clarification Question)	ICER incremental (£/QALY)
Original base case: selpercatinib versus lenvatinib		34,651
Piecewise exponential selected to model OS for all treatments	Piecewise exponential selected to model OS for all treatments with an adjustment applied to the selpercatinib OS to more closely align with UK clinical expert estimates (Clarification Question B1)	36,958
25-year time horizon	35-year time horizon (Clarification Question B4)	33,608
Updated base case: selpercatinib versus lenvatinib		**36,329**
Original base case: selpercatinib versus BSC		43,132

Piecewise exponential selected to model OS for all treatments	Piecewise exponential selected to model OS for all treatments with an adjustment applied to the selpercatinib OS to more closely align with UK clinical expert estimates (Clarification Question B1)	45,047
25-year time horizon	35-year time horizon (Clarification Question B4)	42,181
Updated base case: selpercatinib versus BSC		**44,460**

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

A.1 Severity

In line with the approach taken in the CS, the severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR) and Lumanity was used to calculate the absolute and proportional severity modifiers.[23] A In line with the NICE reference case, the Hernandez-Alava 2017 study, which mapped the EuroQol 5-dimensions 5-levels (EQ-5D-5L) to the 3L, was used (Table 21).[24, 25]

The results demonstrate that for the *RET*-mutant MTC population, selpercatinib is eligible for a 1.2x severity modifier when compared to both cabozantinib and BSC. In the *RET*-fusion positive TC population, selpercatinib is eligible for a 1.2x severity modifier when compared with BSC but is not eligible for a severity modifier versus lenvatinib (Table 21). Therefore, conclusions of the severity modifier calculations are the same with respect to the original company base case.

Table 21: Summary of QALY shortfall analysis

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
RET-mutant MTC				
14.34	Cabozantinib: 2.11	12.23	85.29%	1.2
14.34	BSC: 1.52	12.82	89.40%	1.2
RET-fusion positive TC				
13.38	Lenvatinib: 2.63	10.76	80.35%	1
13.38	BSC: 1.28	12.11	90.44%	1.2

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

A.2 Base-case cost-effectiveness analysis results

Probabilistic base case results

A summary of the probabilistic base case analysis for *RET*-mutant MTC and *RET* fusion-positive TC is presented below.

In line with the approach taken in the CS, 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 may be found in the cost-effectiveness model provided alongside this submission. 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 comparisons for selpercatinib versus cabozantinib and BSC have been conducted for the base case. A summary of the base-case pairwise comparisons for selpercatinib (at PAS price) versus cabozantinib and BSC in *RET*-mutant MTC are presented in Table 22 and Table 25, with net health benefit (NHB) results presented in Table 23 and Table 26 (at selpercatinib PAS price). For reference, results of a fully incremental analysis (at selpercatinib PAS price) are presented in Table 24 and Table 27.

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 £89,785 for patients treated with cabozantinib (an incremental cost of £[redacted]), and £17,110 for patients treated with BSC (an incremental cost of £[redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with 2.11 for patients treated with cabozantinib (an incremental QALY gain of [redacted]) and 1.52 for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of £35,852 and £47,349 per QALY gained versus cabozantinib and BSC, respectively. At a willingness-to-pay threshold (WTP) of £30,000, the NHBs for selpercatinib versus cabozantinib and selpercatinib versus BSC is negative ([redacted] and [redacted]), however this does not take into account the severity modifier. However, as highlighted in Appendix A.1, selpercatinib is eligible for a 1.2x severity modifier when compared with cabozantinib and BSC.

The results presented include the confidential PAS discount provided alongside this submission. It should also be noted that cabozantinib is associated with a simple discount PAS which is not visible to the Company, therefore, cost effectiveness analyses are based upon list prices for all active interventions other than selpercatinib.

Table 22: Pairwise probabilistic base-case results for selpercatinib in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYG[a]	Incremental QALYs[a]	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	89,785	3.409	2.11	[redacted]	[redacted]	[redacted]	35,852
BSC	17,110	2.684	1.52	[redacted]	[redacted]	[redacted]	47,349

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTC: medullary thyroid cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; RET: rearranged during transfection.

Table 23: Probabilistic net health benefit for selpercatinib in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	NHB at £20,000[a]	NHB at £30,000[a]
Selpercatinib	[redacted]	[redacted]	-	-	-	-
Cabozantinib	89,785	2.11	[redacted]	[redacted]	[redacted]	[redacted]
BSC	17,110	1.52	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTC: medullary thyroid cancer; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; RET: rearranged during transfection.

Table 24: Fully incremental probabilistic base-case results for *RET*-mutant MTC (at selpercatinib PAS price)

	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	17,110	1.52	-	-
Cabozantinib	89,785	2.11	Extendedly dominated	123,177
Selpercatinib	[redacted]	[redacted]	47,349	47,349

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

Table 25: Pairwise deterministic base-case results for selpercatinib in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYG[a]	Incremental QALYs[a]	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	89,900	3.35	2.08	[redacted]	[redacted]	[redacted]	35,656
BSC	17,089	2.67	1.51	[redacted]	[redacted]	[redacted]	47,377

[a] Pairwise versus selpercatinib.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTC: medullary thyroid cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; RET: rearranged during transfection.

Table 26: Deterministic net health benefit for selpercatinib in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	NHB at £20,000[a]	NHB at £30,000[a]
Selpercatinib	[redacted]	[redacted]	-	-	-	-
Cabozantinib	89,900	2.08	[redacted]	[redacted]	[redacted]	[redacted]
BSC	17,089	1.51	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTC: medullary thyroid cancer; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; RET: rearranged during transfection.

Table 27: Fully incremental deterministic base-case results for *RET*-mutant MTC (at selpercatinib PAS price)

	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	17,089	1.51	-	-
Cabozantinib	89,900	2.08	Extendedly dominated	127,355
Selpercatinib	[redacted]	[redacted]	47,377	47,377

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

An overview of the pairwise probabilistic base-case cost-effectiveness results for the *RET* fusion-positive TC population can be found in Table 28 and Table 31 (at selpercatinib PAS price), with NHB results presented in Table 29 and Table 32. In line with the approach taken for the *RET*-mutant MTC population, results of a fully incremental cost-effectiveness analysis are presented in Table 30 and Table 33 (at selpercatinib PAS price).

The base case cost-effectiveness results show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be £[redacted] compared with £96,510 for patients treated with lenvatinib (incremental cost of £[redacted]) and £[redacted] for patients treated with BSC (incremental costs are £[redacted]).

The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with 2.63 for patients treated with lenvatinib (an incremental QALY gain of [redacted]), resulting in an ICER of £36,347 per QALY gained versus lenvatinib. The total QALYs for patients receiving BSC are estimated to be [redacted] for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER for selpercatinib of £44,429 per QALY gained versus BSC. The NHB at a £30,000 WTP is negative for both lenvatinib and BSC ([redacted] and [redacted], respectively). As highlighted in Appendix A.1, selpercatinib is eligible for a 1.2x severity modifier when compared with BSC. This severity modifier is not included in these cost-effectiveness results.

The results presented include the confidential PAS discount provided alongside this submission. It should also be noted that lenvatinib is associated with a simple discount PAS which is not visible to the Company, therefore, cost effectiveness analyses are based upon list prices for all active interventions other than selpercatinib.

Table 28: Pairwise probabilistic base-case results for selpercatinib versus lenvatinib and BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Lenvatinib	96,510	4.136	2.63	[redacted]	[redacted]	[redacted]	36,347
BSC	15,983	2.306	1.28	[redacted]	[redacted]	[redacted]	44,429

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

Table 29: Probabilistic net health benefit for selpercatinib versus lenvatinib and BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	NHB at £20,000[a]	NHB at £30,000[a]
Selpercatinib	[redacted]	[redacted]	-	-	-	-
Lenvatinib	96,510	2.63	[redacted]	[redacted]	[redacted]	[redacted]
BSC	15,983	1.28	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; RET: rearranged during transfection; TC: thyroid cancer.

Table 30: Fully incremental probabilistic base-case results for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	15,983	1.28	-	-
Lenvatinib	96,510	2.63	Extendedly dominated	59,649
Selpercatinib	[redacted]	[redacted]	44,429	44,429

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

Table 31: Pairwise deterministic base-case results for selpercatinib versus lenvatinib and BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)[a]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Lenvatinib	96,507	4.13	2.62	[redacted]	[redacted]	[redacted]	36,329
BSC	16,030	2.30	1.27	[redacted]	[redacted]	[redacted]	44,460

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

Table 32: Deterministic net health benefit for selpercatinib versus lenvatinib and BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	NHB at £20,000[a]	NHB at £30,000[a]
Selpercatinib	[redacted]	[redacted]	-	-	-	-
Lenvatinib	96,507	2.62	[redacted]	[redacted]	[redacted]	[redacted]
BSC	16,030	1.27	[redacted]	[redacted]	[redacted]	[redacted]

[a] Pairwise versus selpercatinib.
Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; RET: rearranged during transfection; TC: thyroid cancer.

Table 33: Fully incremental deterministic base-case results for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	ICER (QALYs) vs previous non-dominated alternative	ICER (QALYs) vs BSC
BSC	16,030	1.27	-	-
Lenvatinib	96,507	2.62	Extendedly dominated	59,597
Selpercatinib	[redacted]	[redacted]	44,460	44,460

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

A.3 Probabilistic sensitivity analysis

RET-mutant MTC

Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves versus cabozantinib and BSC are presented in Figure 4 and Figure 5.

Figure 4: Cost-effectiveness plane scatterplot for selpercatinib versus cabozantinib and BSC – *RET*-mutant MTC (at selpercatinib PAS price)

Generated using 1,000 iterations of the PSA.
Abbreviations: MTC: medullary thyroid cancer; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

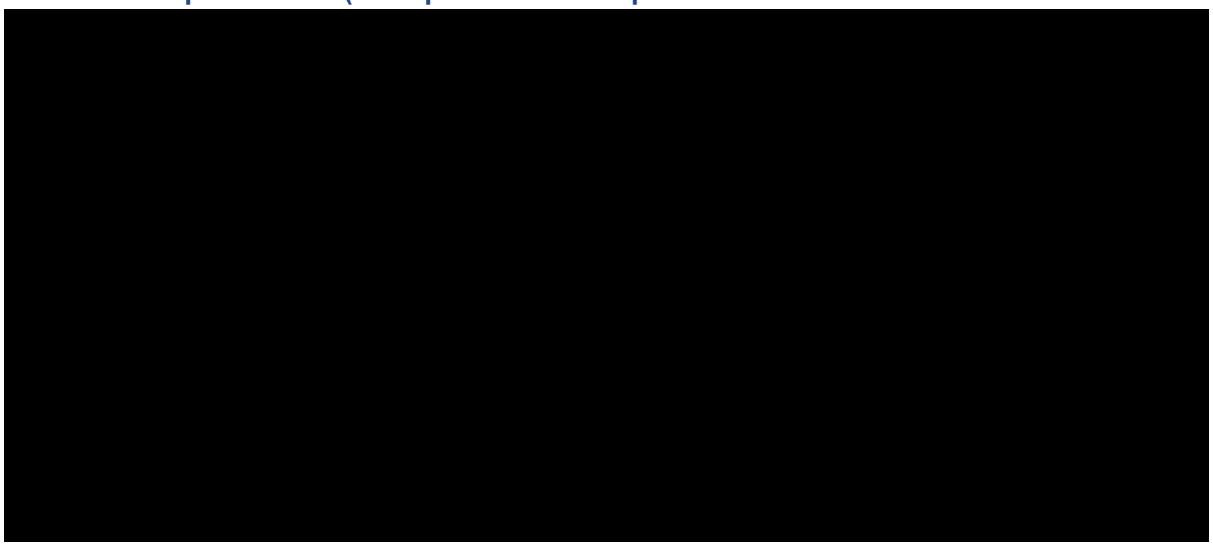
Figure 5: Cost-effectiveness acceptability curves for selpercatinib versus cabozantinib and BSC – *RET*-mutant MTC (at selpercatinib PAS price)

Generated using 1,000 iterations of the PSA.
Abbreviations: MTC: medullary thyroid cancer; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

RET fusion-positive TC

Cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves for selpercatinib versus lenvatinib and BSC are presented in Figure 6 and Figure 7.

Figure 6: Cost-effectiveness plane scatterplot for selpercatinib versus lenvatinib and BSC – *RET* fusion-positive TC (at selpercatinib PAS price



Generated using 1,000 iterations of the PSA.
Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

Figure 7: Cost-effectiveness plane scatterplot for selpercatinib versus lenvatinib and BSC – *RET* fusion-positive TC (at selpercatinib PAS price)

Generated using 1,000 iterations of the PSA.
Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

A.4 Deterministic sensitivity analysis

RET-mutant MTC

The 25 most influential variables in the deterministic sensitivity analyses (DSA) for the analysis of selpercatinib versus cabozantinib and selpercatinib versus BSC are presented as tornado plots in Figure 8 and Figure 9, respectively. Placeholder: The most influential parameters were the discount rate for costs and outcomes, the progression-free health state utility value and the progression-free health state costs. For the comparison of selpercatinib versus cabozantinib, the OS for cabozantinib represents another influential parameter.

Figure 8: Tornado plot (ICER) of selpercatinib versus cabozantinib – *RET*-mutant MTC (at selpercatinib PAS price)

Abbreviations: ICER: incremental cost-effectiveness ratio; MTC: medullary thyroid cancer; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

Figure 9: Tornado plot (ICER) of selpercatinib versus BSC – *RET*-mutant MTC (at selpercatinib PAS price)

Abbreviations: BSC: best supportive care; ECG: echocardiogram; ICER: incremental cost-effectiveness ratio; MTC: medullary thyroid cancer; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection.

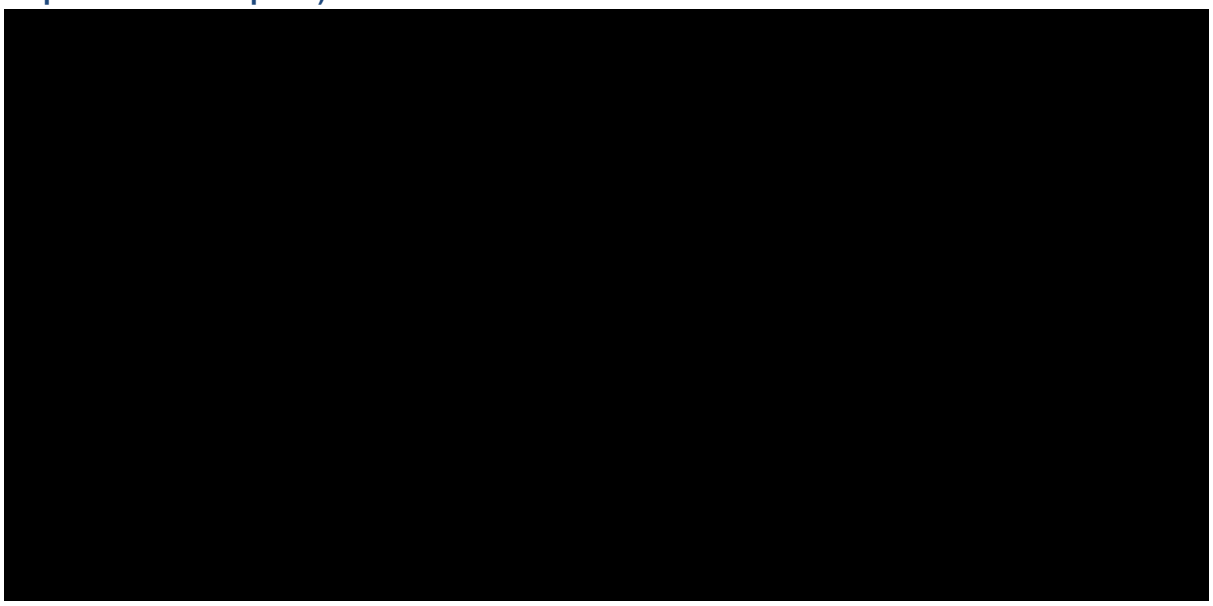
RET fusion-positive TC

The 25 most influential variables in the DSA for the analysis of selpercatinib versus relevant comparators are presented as a tornado plot in Figure 10 and Figure 11. Placeholder: The most influential parameters were the discount rate for outcomes and costs, the progression-free health state utility value and the progression-free health state costs.

Figure 10: Tornado plot (ICER) of selpercatinib versus lenvatinib – *RET* fusion-positive TC (at selpercatinib PAS price)

Abbreviations: BSC: best supportive care; ECG: echocardiogram; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; RET: rearranged during transfection; TC: thyroid cancer

Figure 11: Tornado plot (ICER) of selpercatinib versus BSC – *RET* fusion-positive TC (at selpercatinib PAS price)



Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality adjusted life year; RET: rearranged during transfection; TC: thyroid cancer.

Appendix B: Technical appendix

As outlined in response to Clarification Questions B1 and B2, the base case has been updated to apply an adjustment factor to the selpercatinib OS curves.

RET-mutant MTC

The application of the adjustment factor is user-adjustable, with the magnitude of the adjustment and start point of the adjustment being applied on the 'Survival – MTC' sheet, cells D74 and D76, respectively. The adjustment can also be unselected in cell D71.

The adjustment is applied in the 'MTC S(t) (2)' sheet. Two additional columns have been included on this sheet for the selpercatinib hazard rate (Column T) and survival probabilities (Column U). The adjustment factor is applied to the hazard rate, calculated from the original parametric model-based survival probabilities (Column S), resulting in modified survival probabilities in Column U.

The formula applied in column T is as follows:

$$= \mathrm{IF}(\mathrm{AND}(\$U\$4 = 1; B12 >= 'Survival\ -\ MTC'!\$D\$74); \mathrm{IF}(S13 = 0; 0; -\mathrm{LN}(S13) - (-\mathrm{LN}(S12))) * 'Survival\ -\ MTC'!\$D\$76; \mathrm{IF}(S13 = 0; 0; -\mathrm{LN}(S13) - (-\mathrm{LN}(S12))))$$

The formula applied in column U is as follows:

$$S(t)\ = \mathrm{EXP}(-\mathrm{SUM}(T\$9{:}T10)$$

RET fusion-positive TC

The application of the adjustment factor is user-adjustable, with the magnitude of the adjustment and start point of the adjustment being applied on the 'Survival – TC' sheet, cells D60 and D62, respectively. The adjustment can also be unselected in cell D57.

The adjustment is applied in the 'TC S(t) (2)' sheet. Two additional columns have been included on this sheet for the selpercatinib hazard rate (Column N) and survival probabilities (Column O). The adjustment factor is applied to the hazard rate, calculated from the original parametric model-based survival probabilities (Column M), resulting in modified survival probabilities in Column O.

The formula applied in column N is as follows:

$$= \mathrm{IF}(\mathrm{AND}(\$O\$3 = 1, B10 >= 'Survival\ -\ TC'!\$D\$60), \mathrm{IF}(M11 = 0,0, -\mathrm{LN}(M11) - (-\mathrm{LN}(M10))) * 'Survival\ -\ TC'!\$D\$62, \mathrm{IF}(M11 = 0,0, -\mathrm{LN}(M11) - (-\mathrm{LN}(M10))))$$

The formula applied in Column O is as follows:

$$S(t)\ = \mathrm{EXP}(-\mathrm{SUM}(N\$10{:}N11)$$

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Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132] – Addendum to clarification questions response

Landmark OS estimates for the piecewise exponential OS extrapolation for selpercatinib – *RET* fusion-positive TC population

Following the response to Clarification Questions, a reporting error was identified in the original Company Submission (CS) and the External Assessment Group (EAG) Clarification Questions response. This relates to the landmark overall survival (OS) estimates predicted by the piecewise exponential curve for selpercatinib in thyroid cancer (TC) reported in Table 74, Section B.3.3.4 of the CS and Table 17, Clarification Question B2 of the EAG Clarification Questions response.

Lilly apologise for this error and have provided an addendum to the Clarification Questions response to provide the correct values. Although the piecewise exponential curve was selected as the base case OS extrapolation in the rearranged during transfection (*RET*) fusion-positive TC population, Lilly can confirm that this error did not impact the revised company base case or the revised cost-effectiveness model submitted in response to the EAG Clarification Questions. With the exception of the piecewise exponential OS curve, all other landmark estimates presented in the original CS were correct.

Table 1 presents the corrected median OS and landmark OS estimates at 5, 10 and 20 years for patients with *RET* fusion-positive TC treated with selpercatinib based on the piecewise exponential model, both with and without the adjustment factor applied. The response to Clarification Question B2 reported the correct median and landmark rates of OS using the piecewise exponential curve for TC with the 1.2x adjustment factor applied.

Table 1: Corrected landmark OS estimates with and without adjustment for selpercatinib OS in *RET* fusion-positive TC

Parametric curve	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Clinical expert estimates				
NA	NA	NA	35–50	5–15
Revised company base case				
Piecewise exponential (no adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential (1.2 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA: not applicable; OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.

Cabozantinib OS extrapolations in the *RET*-mutant MTC population

Lilly would also like to highlight that in the original CS, a figure presenting the modelled OS extrapolation for cabozantinib only was included (Figure 40, Section B.3.3.3); this extrapolation was based on the OS hazard ratio (HR) for cabozantinib versus placebo (a proxy for BSC) applied to the best supportive care extrapolation. For completeness, all OS extrapolations explored for cabozantinib (derived by the application of the OS HR for cabozantinib versus placebo) are presented in Figure 1.

Figure 1: Extrapolations of OS – Cabozantinib, *RET*-mutant MTC

Abbreviations: CS: company submission; MTC: medullary thyroid cancer; OS: overall survival; Prop: proportion; RET: rearranged during transfection.

The median OS and landmark OS estimates pertaining to the Stratified Spline Knot 2 extrapolation curve presented in Figure 1 were erroneously excluded from the CS for cabozantinib; these values were also excluded for selpercatinib and BSC. However, the landmark estimates of survival for all treatments were not plausible when compared to the clinical expert estimates of survival, with the stratified spline knot 2 extrapolation predicting [redacted]%, [redacted]% and [redacted]% of patients to be alive at 20 years for selpercatinib, cabozantinib and BSC, respectively. As such, exclusion of this curve had no impact on the choice of OS extrapolation for the company base case.

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Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Association for Multiple Endocrine Neoplasia Disorders / AMEND
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	We contacted members of AMEND via our private social media groups, as well as other relevant social media groups and asked those with genetic or sporadic medullary thyroid cancer (MTC) to complete a short survey related to the questions on this submission template. AMEND only covers medullary thyroid cancer and therefore other RET-driven thyroid cancers are not included in this submission. We received 22 complete responses (18 from England and 4 from Scotland). 19 respondents were patients themselves, 2 are parents/carers, and 1 is a family member of someone with MTC. 17 people have advanced MTC.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The most impactful problems on life for those with metastatic MTC range from fatigue (the greatest issue), through to diarrhoea, then pain and swallowing problems. A respondent also included severe anxiety and this is additionally reflected throughout their comments, some of which are included below: 'Before treatment, advanced MTC caused extreme fatigue, severe diarrhoea, anxiety and depression symptoms, breathlessness on exertion, pain and weight loss. This all had a negative effect on education and well-being due to ill-health, meaning lots of school missed and unable to join peers.' (mother of teenager with metastatic MTC) 'Unable to work full time and had to take extended periods of sick leave. Difficult-to-control diarrhoea and fatigue resulting in significantly worse quality of life compared to pre-diagnosis. Continued psychological distress due to lack of curative / significantly life-extending treatments and no hope of a normal QOL in the future….Chronic diarrhoea also has a big negative impact on maintaining dignity, due to the scope for accidents or the embarrassment and worry about even leaving the house. Many days I cancelled plans with friends/family or could not attend work due to being symptomatic (both physically and mentally).' (adult patient) 'My mum became horrendously depressed. Her life was made so much smaller…Everyday was a battle to get what she needed….She became profoundly disabled, unable to speak… She was in the waiting list for counselling for over 3 years and died without receiving a single session. Symptom management was down to me to advocate for and that was hit and miss.' (carer) 'MTC significantly affected my daily life before treatment. I was in a lot of pain, with fatigue, and had unmanageable diarrhoea that left me unable to leave home and impacted on my ability to work.' (adult patient) 'I am unable to work due to the aggressive neck surgery affecting the strength in my arms. I'm struggling with the diarrhoea and have frequent accidents with soiling myself. The distress mentally just gets worse as the disease progresses and I have started on antidepressants….I'm mentally struggling with anxiety and depression due to the diarrhoea that is confining me to the home for fear of soiling myself and I will starve myself if going to a hospital appointment to try and prevent an accident.' (adult patient)

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	40% of respondents to our survey believe that the current treatments/care available on the NHS are 'good' (excellent = 9%, average = 22%, poor = 9%, very poor = 18%). One patient commented that they would have rated it 'excellent' if you can get selpercatinib. Many patients cited lack of knowledge of medical staff about MTC as a significant factor in their lower ratings.
8. Is there an unmet need for patients with this condition?	The main unmet needs for patients with this condition are • Earlier diagnosis • access to a wider variety of treatments • more research into these cancers • a better understanding of the disease amongst medical staff • symptom and/or drug side effect management and control 'Access to selpercatinib for RET patients at diagnosis of advanced MTC and access to the next generation RET targeted drugs when selpercatinib stops working and a relevant mutation is found.'

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	81% of our survey respondents were aware of selpercatinib. Several patients commented that selpercatinib provides 'hope', both for their own futures living with their diseases, but also for the development of similar technologies in the future. In addition, they highlight ease of administration and the dramatic, positive effects and lack of severe side effects experienced: 'Low to no side effects. Able to maintain an excellent quality of life. Longevity of progression free treatment.' 'It has been a very kind treatment. Only side effect so far has been a drug mouth. Felt an immediate improvement from day 1 of taking it. It was a noticeable improvement in symptoms. The benefit of selpercatinib has been immense. I am able to attend college, travel and enjoy my passion for music. I no longer use a wheelchair. My diarrhoea has stopped. I have gained much-needed weight. I no longer have anxiety symptoms and am enjoying the life it has given me. It is easy to take, just 2 pills, twice a day. My tumours have shrunk and remains table after almost 4 years of treatment. My extremely high calcitonin and CEA have dramatically reduced on selpercatinib and continue to reduce.'

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	16 people responded to this question. The majority commented that there were no disadvantages to selpercatinib. However, a few acknowledged that side effects could be a problem if not managed effectively. One person also acknowledged that it was not suitable for those whose thyroid cancer was not RET-driven.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	11 people answered this question, many recognising that RET+ve patients would benefit most and that RET-ve patients least. They also highlighted that those who suffer severe side effects from cabozantinib would likely benefit. 'RET+ patients would benefit most as it is targeted at RET. Those with advanced disease at diagnosis given selpercatinib as early as possible would gain the most.' 'People who do not respond well to or tolerate the currently available first line treatment would benefit from this being made available. In an ideal world this would be a first line treatment due to the HUGE difference it makes to people's quality of life and overall day-to-day health and well-being, when compared with current first line treatments.'

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	12 people answered this question: 'Children should have access to this drug as well as adults.' This is in reference to those with hereditary MTC syndromes such as multiple endocrine neoplasia type 3 (MEN3, AKA MEN2B), which children are usually diagnosed with MTC at a very young age. 'Access to MTC specialists to diagnose and prescribe is not necessarily a level playing field across the UK which may result in unintended inequalities.' 'Yes, if someone is underweight and suffering from diarrhoea daily, then they should be able to go on selpercatinib.'

Other issues

13. Are there any other issues that you would like the committee to consider?	'I don't think my son would still be alive without being on selpercatinib. He was very poorly by the time he was given it on compassionate grounds. It has given him a much better quality of life and, in my opinion, extended his life. I hope it is made available as a first line treatment on the NHS for RET+ patients as it is a far superior and kinder treatment than currently available on the NHS.' 'I am on selpercatinib and have been since May 2021. I'm on the LIBRETTO trial. I have been living a 'fairly normal' life since then. MTC is a difficult cancer to live with as we do not have many treatment options and as it's rare we can feel quite isolated. I feel as though I am treading on water in the hope of another drug becoming available, for when selpercatinib fails for me. I am very grateful to have been given this extra time the drug has allowed, and I will keep hoping it gives me lots more time to see my children grow up.'

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• metastatic MTC results in a range of serious side effects that have a huge negative impact on quality of life • the current first-line treatment (cabozantinib) has serious side effects that, unless well managed, may have similar negative impact on quality of life • patients are well aware of selpercatinib and its reputation for less severe side effects • patients feel that selpercatinib should be made first line in metastatic RET+ve disease • parents of children with genetic, metastatic MTC feel that selpercatinib should be made first line in these cases

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted] (BTF) [redacted] (BTCT)
2. Name of organisation	British Thyroid Foundation (BTF) Butterfly Thyroid Cancer Trust (BTCT)
3. Job title or position	[redacted] of BTF [redacted] of BTCT
4a. Brief description of the organisation (including who funds it). How many members does it have?	The BTF was established in 1991 and is registered as a charity in England and Wales (No: 1006391) and Scotland (SC046037). The organisation provides information and support to people with thyroid disorders, and helps their families and carers, and the wider population to understand the condition. The BTF is a membership organisation and currently has approximately 2,500 members. Patients receive peer support through our volunteer-run telephone helpline, as well as through the resources provided on the BTF website (http://www.btf-thyroid.org/) and online support forums. The majority of the BTF's funding comes from membership subscriptions, donations and community fundraising. No pharmaceutical companies are corporate members of the BTF. Within the last two years the only donation the BTF has received from a pharmaceutical company has been in April 2023 from argenx who made grant of £5,000 towards the work we do to raise awareness and support for patients with Thyroid Eye Disease. BTCT is the only registered charity in England dedicated solely to providing information and support to people affected by thyroid cancer. It was set up in response to a paucity of information available when Kate Farnell, CEO, was diagnosed and treated for thyroid cancer in 2000. There has been a dedicated telephone helpline available from the inception of the charity for over 20 years, over which time we have answered thousands of calls from a vast cross section of people affected by thyroid cancer. To this end we have huge first-hand experience of how thyroid cancer affects patients and their loved ones.

	The organisation has a ‘holiday lodge’ for families requiring respite. We provide up to date patient information via our patient friendly website, leaflets, folders and DVDs, all are free of charge to patients and hospital clinics. Our information is BMA approved. Kate Farnell has worked in a voluntary role as ‘Thyroid Cancer Patient advisor’ within the thyroid cancer team at Freeman Hospital, Newcastle upon Tyne for over 15 years, she has an honorary contract with the Trust and as such is part of the care team. This a unique role/patient/doctor partnership and has led to many awards for the charity. Kate has a vast wealth of experience supporting those patients with non-resectable, advanced, metastatic medullary thyroid cancer (MTC). Kate was lead in the first multi-national workshop on the use of Tyrosine-Kinase Inhibitors (TKIs) and what this means for patients. There was global representation from leading clinicians, patient organisations and importantly, two terminally ill patients attended to tell their thyroid cancer stories. BTCT is funded via donations only and an annual grant from The Syncona Foundation. They have members but membership is free.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No (BTF) No (BTCT)

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	BTF is a patient organisation that supports people living with all thyroid disorders and BTCT is dedicated solely to patients who have been diagnosed with thyroid cancer. Most people who are diagnosed with this disease and are treated in the UK will be signposted to our charities. Both organisations have a telephone helpline and run online forums where we engage with people who unfortunately have been diagnosed with advanced thyroid cancer. BTCT has a dedicated help line with a patient support lead who listens to and supports these patients every week, in doing so she hears what these patients are dealing with on an daily basis. To prepare this submission we have referred to the experiences patients have shared with us in recent years. We also posted a message on social media (Facebook and Twitter) and invited people who have been treated with this medicine to get in touch and let us know how it affected them. One male patient contacted us in response to our request for personal experiences of this treatment. He has been taking it as part of the LIBRETTO-531 trial for over two years.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Thyroid cancer typically metastasizes locally in the neck, bones, lungs, liver and brain. The small group of patients eligible for this drug have metastatic disease, which is progressive and unresponsive to other standard treatments. Metastatic disease can therefore be associated with symptoms such as bone pain, swallowing difficulties and breathing difficulties, a reduction in activities of daily living and quality of life. Progressive disease also causes these symptoms plus potential voice change. The psychological impact of this disease can also be substantial with low mood and fatigue commonly reported. Patients will often require support and care to assist with daily functions and to attend hospital appointments. The patient we spoke to described how he had a broken arm as a result of the cancer having spread to the bones in his arm. Even though it had been operated on and he had a pin in it he had virtually lost the use of his arm. As this had happened during COVID he hadn't been able to access physiotherapy which has worsened his situation. Most patients will no longer be able to work and are likely to be isolated socially as they are unable to continue their usual activities. The natural history of thyroid cancer is such that this group of patients may survive longer than patients with other metastatic cancers, but with a poor quality of life. A female patient wrote about her life with the disease: *'As with any cancer it is very difficult to live with not knowing how things are going to go. It's like waking up every day under a black cloud. My cancer can never be cured but can be held back and stable but for how long nobody knows. This is difficult to deal with. I sometimes feel isolated as there does not seem to be enough information or talk about thyroid cancer as compared to the more common cancers.*' Another woman made the following points: *'It is difficult to plan ahead and it's hard to switch off from my condition. Even though I am 75, I love life. I don't enjoy discussing my condition, or even telling anyone about it at the present time. Only our family and closest friends know.'*

	It is worth stressing that if patients respond to these new targeted treatments their symptoms can significantly reduce, allowing them to increase their level of activity, be more independent, improve mental wellbeing, improve their quality of life, and potentially allow reduction in pain relief. Importantly some people also benefit long term and it's not just a short period of improvement that is seen. Some patients could be on treatment with maintained quality of life and independence for several years. Patients handle this scenario differently and in an individual manner. Some cope well and look on the bright side, for example being grateful for having more years than anticipated when diagnosed. Others do not cope at all and battle related depression on top of the disease.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Many patients with advanced thyroid cancer who have been treated with lenvatinib and sorafenib have had very positive results. The outcomes that are important to patients when having these treatments include better symptom control and management of the pain, and this in turn ideally offers people an improved quality of life and more time to spend with their family and friends. Some patients may also be able to return to work and other family or social commitments that had previously been interrupted by the disease. One patient told us *'Obviously the most important outcome would be to be cancer free but I know this will never happen to me so it's important for me to have the best treatment available.'* One lady told us: *'I am currently being treated with Lenvatinib which has been ongoing for three and a half years, after 2 years of RAI treatment that has become ineffective. Lenvatinib has been successful on a couple of the tumours but I have one still persisting that has not changed now for over a year. I would love to have something else that could be used to help my long journey with Thyroid Cancer. Selpercatinib is my only hope for the future and the thought that I may not get access is frankly terrifying.'* However, the drugs that are currently available often cause significant side effects, including hypertension, hand and foot skin reactions, fatigue, constipation, diarrhoea, nausea and vomiting. Not all patients experience severe side effects but for some they cannot be tolerated and it will be necessary to reduce the dose, have a break from treatment, or stop taking the drug altogether. One patient told us that although the side effects of the drug he took were very challenging, his attitude was that having cancer requires you to make many compromises and these were the ones he was prepared to make to survive.

8. Is there an unmet need for patients with this condition?	Advanced thyroid cancer is fortunately very rare. But as there are such small numbers of patients who are affected, research into new treatments is challenging and has been very limited. The consequence of this is that there are few treatment options for these patients when compared to those who are diagnosed with the more common cancers. Patients often describe to us the loss of hope they feel when all treatments options had been exhausted. One lady told us she had had five surgeries, a severe (surgery related) infection, loss of a vocal cord, long periods in hospital, and radiotherapy. When told by her consultant that there was nothing more that could be done, she wrote: '*Can you imagine how my husband and I felt as we walked out of that clinic? After going through all I'd been through over a space of three years I was totally at rock bottom. What is the point of life if there is no hope?'* We strongly support the availability of this medicine that may offer improved outcomes for this small group of patients who are currently so disadvantaged. One lady wrote to us *'I'm determined to continue to be optimistic but I need to know there is hope for new drugs to be available when I need them.'*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We understand that patients who have been treated with selpercatinib have had better progression free survival than those who have had other TKIs, including lenvatinib. We also welcome evidence that suggests patients have found this drug is much better tolerated with significantly fewer side effects than the alternative TKIs. The patient we spoke to described how within a short time of starting treatment with selpercatinib he had regained the use of his arm that prior to this he couldn't use at all. Also that the tumour in his abdomen has continued to shrink, even on the latest scan, two years after commencing treatment. '*The improvement was brilliant….This drug is the best thing that's happened to me since I was diagnosed with cancer and I'm over the moon with the response….. I definitely have more energy and some days I don't even think about the fact that I have cancer. For me it's a win-win situation.'* Apart from a few small changes in lifestyle he feels that this treatment has enabled him to continue his life as normal.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The patient we spoke to told us the side effects he has experienced whilst on this treatment have been easily manageable. He sometimes gets acid reflux which he didn't used to get. He also has some photosensitivity and skin rashes so cannot spend time fishing which he used to enjoy. But he says this is a small price to pay. By adjusting the dose he feels that the side effects he has had have been straightforward for him to deal with.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not that we are aware of.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The patients who might benefit from this treatment are a very small, precisely targeted cohort and evidence suggests they will have a longer period of progression-free survival than with the currently available treatments. • Patients find this drug easier to tolerate than currently available treatments so are more likely to be able to use it for longer and achieve the potential benefits. • The treatment offers patients the potential for improvements to quality of life, self-esteem, and emotional wellbeing as well as a significant reduction in symptoms and increased activity levels. • The availability of this medicine gives patients and family members hope for the future which is likely to increase their confidence, and make it more likely that they can contribute to family life and wider society, and even return to work.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136152

Completed 15 January 2024

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Selpercatinib for untreated advanced thyroid cancer with *RET* alterations [ID6132]

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Date completed: 15 January 2024

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136152

Acknowledgements: The authors would like to thank Ehab Ibrahim, Consultant Oncologist, The Clatterbridge Cancer Centre, Liverpool who provided feedback on a draft version of 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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: None.

Declared competing interests of the peer reviewers: None.

This report should be referenced as follows: Bresnahan R, Fleeman N, Mahon J, Bryning S, Chaplin M, Boland A, Beale S, Marsden A, Dundar Y, Brammer C. Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]: A Single Technology Appraisal. LRiG, University of Liverpool, 2024

Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
Nigel Fleeman	Critical appraisal of the clinical evidence
James Mahon	Critical appraisal of the economic evidence
Sam Bryning	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the statistical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Ashley Marsden	Critical appraisal of the company submission
Yenal Dundar	Critical appraisal of the review methods
Caroline Brammer	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AIC	Akaike Information Criteria
ALT	alanine aminotransferase
BIC	Bayesian Information Criteria
BID	twice daily
BSC	best supportive care
CDF	Cancer Drugs Fund
CI	confidence interval
CR	complete response
CS	company submission
CSR	clinical study report
DCO	data cut-off
DoR	duration of response
EAG	External Assessment Group
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30
EQ-5D	EuroQol-5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy – General
HR	hazard ratio
HRQoL	health-related quality of life
ICER	Incremental cost effectiveness ratio
IRC	Independent Review Committee
ITCs	indirect treatment comparisons
ITT	intention-to-treat
K-M	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
MDASI	Monroe Dunaway Anderson Symptom Inventory
MKI	multi-kinase inhibitor
mSTIDAT	modified version of the Systemic Treatment-Induced Diarrhoea Assessment Tool
MTA	Multiple Technology Appraisal
MTC	medullary thyroid cancer
NGS	next generation sequencing
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressed disease
PF	progression-free
PFS	progression-free survival
PH	proportional hazards
PR	partial response

QALY	quality adjusted life year
QD	once daily
RDI	relative dose intensity
RET	rearranged during transfection
RPSFT	rank-preserving structural failure time
SLR	systematic literature review
SmPC	summary of product characteristics
TC	thyroid cancer subtypes that develop in follicular cells
TFFS	treatment failure-free survival
TKI	tyrosine kinase inhibitor
TLR	targeted literature review
TSAP	trial statistical analysis plan
VAS	visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER per QALY gained. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table A Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Clinical effectiveness evidence limitations	Section 2.4, Section 2.5.1 to Section 2.5.3, Section 3.3.1, Section 3.6, Section 3.7.4, Section 3.10.1, Section 3.10.6, Section 3.11.6 and Section 3.14
Issue 2	*RET*-mutant MTC population: limitations of company MAICs	Section 2.5.1, Section 2.5.3, , Section 3.10.4 and Section 3.14
Issue 3	*RET* fusion-positive TC population: limitations of company naïve unadjusted indirect treatment comparisons	Section 2.5.1, Section 2.5.3, Section 3.11.1, Section 3.11.4, Section 3.11.6 and Section 3.14
Issue 4	Uncertainty around selpercatinib safety evidence	Section 2.4, Section 2.5.2, Section 3.9 and Section 3.14
Issue 5	*RET*-mutant MTC and *RET* fusion-positive TC populations: selpercatinib overall survival estimates	Section 6.2.1 and Section 6.2.2
Issue 6	*RET*-mutant MTC population: cabozantinib overall survival estimates	Section 6.2.1
Issue 7	Cabozantinib and lenvatinib drug costs: use of RDI rather than adherence data	Section 6.4
Issue 8	*RET*-mutant MTC and *RET* fusion-positive TC populations: health state utility values	Section 6.5
Issue 9	*RET*-mutant MTC population: severity modifier calculation	Section 6.6

MAIC=matching-adjusted indirect comparison; MTC=medullary thyroid cancer; OS=overall survival; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are related to long-term overall survival estimates.

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life in a QALY. An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

1.2.1 EAG alternative modelling assumptions that have the greatest effect on the ICER per QALY gained

Table B *RET*-mutant MTC population: EAG assumptions that have the largest impact on the company base case ICER per QALY gained

Comparisons	
Selpercatinib vs cabozantinib	**Selpercatinib vs best supportive care**
Selpercatinib OS estimates	Selpercatinib OS estimates
Distribution used to generate OS estimates for patients treated with cabozantinib	None
Utility values	

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; OS=overall survival; QALY=quality adjusted life year; *RET*=rearranged during transfection

Table C *RET* fusion-positive population: EAG assumptions that have the largest impact on the company base case ICER per QALY gained

Comparisons	
Selpercatinib vs lenvatinib	**Selpercatinib vs best supportive care**
Selpercatinib OS estimates	Selpercatinib OS estimates
Utility values	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year; *RET*=rearranged during transfection

1.3 *The decision problem: summary of the EAG's key issues*

Issue 1 Clinical effectiveness evidence limitations

Report section	Section 2.4, Section 2.5.1 to Section 2.5.3, Section 3.3.1, Section 3.6, Section 3.7.4, Section 3.10.1, Section 3.10.6, Section 3.11.6 and Section 3.14
Description of issue and why the EAG has identified it as important	The following issues are potentially important but may not affect decision-making: • clinical effectiveness evidence for systemic therapy-naïve patients with *RET* fusion-positive TC is limited (n=24) • clinical effectiveness evidence for patients with *RET*-mutant MTC aged 12 to 18 years treated with selpercatinib is limited (LIBRETTO-001 trial: [redacted]; LIBRETTO-531 trial: n=1). There is no clinical effectiveness evidence for patients with *RET* fusion-positive TC aged 12 to 18 years treated with selpercatinib • the company was unable to provide some of the requested LIBRETTO-001 trial inclusion criteria data (Clarification Question A1); this means that it is not clear whether LIBRETTO-001 trial *RET*-mutant MTC and *RET* fusion-positive TC patients are representative of patients who are likely to be treated in the NHS • the company has used placebo arm trial data as a proxy for BSC; however, in the SELECT and DECISION trials, patients were able to receive active treatment (i.e., the intervention) on disease progression • no EMA/MHRA licence for the systemic therapy-naïve *RET* fusion-positive TC population.
What alternative approach has the EAG suggested?	None. Clinical advice to the EAG is that: • available trial data are generalisable to patients aged 12 to 18 years • in NHS practice, most patients suitable for BSC would not be suitable for active treatment.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	None.

BSC=best supportive care; CS=company submission; EAG=External Assessment Group; MHRA=Medicines and Healthcare products Regulatory Agency; NHS=National Health Service; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 2 *RET*-mutant MTC: limitations of company MAICs

Report section	Section 2.5.1, Section 2.5.3, Section 3.10.1, Section 3.10.4 and Section 3.14
Description of issue and why the EAG has identified it as important	The company performed MAICs (selpercatinib versus cabozantinib and versus BSC). These were populated with any-line data from the LIBRETTO-001 trial and any-line data from the EXAM trial. LIBRETTO-001 trial patients had *RET*-mutant MTC. OS results were only available for the EXAM trial *RET* M918T mutation positive subgroup. Therefore, the generalisability of company MAIC results to the population specified in the final scope issued by NICE (i.e., cabozantinib/vandetanib-naïve patients with *RET* mutant MTC) is unclear. The company provided direct clinical effectiveness evidence from the LIBRETTO-531 trial (selpercatinib versus cabozantinib, cabozantinib/ vandetanib-naïve patients with *RET*-mutant MTC). However, the LIBRETTO-001 trial median PFS follow-up ([redacted] months) is longer than the LIBRETTO-531 trial interim analysis, selpercatinib arm median PFS follow-up ([redacted] months).
What alternative approach has the EAG suggested?	The EAG considers that MAIC results generated using selpercatinib data from LIBRETTO-001 trial cabozantinib/vandetanib-naïve patients would be informative (as all EXAM trial patients were cabozantinib-naïve).
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice to assess the impact of *RET* mutation status and line of treatment on clinical effectiveness results. The LIBRETTO-531 trial may provide informative results (estimated completion date is 2026).

BSC=best supportive care; EAG=External Assessment Group; MAIC=matching-adjusted indirect comparison; MTC=medullary thyroid cancer; NICE=National Institute for Health and Care Excellence; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Issue 3 *RET* fusion-positive TC: limitations of company naïve, unadjusted indirect treatment comparisons

Report section	Section 2.5.1, Section 2.5.3, Section 3.11.1, Section 3.11.4, Section 3.11.6 and Section 3.14
Description of issue and why the EAG has identified it as important	Due to a lack of direct evidence, the company performed naïve, unadjusted indirect treatment comparisons (selpercatinib versus lenvatinib, versus sorafenib and versus BSC). Naïve, unadjusted indirect treatment comparisons do not account for differences in baseline patient characteristics and results are highly uncertain and subject to bias. These comparisons were populated with any-line data from the LIBRETTO-001 trial, the SELECT trial and the DECISION trial. LIBRETTO-001 trial patients had *RET* fusion-positive TC. The *RET* mutation status of patients enrolled in the SELECT and DECISION trials is unknown. Therefore, the generalisability of company indirect comparison results to the population specified in the final scope issued by NICE (i.e., systemic therapy-naïve patients with *RET* fusion-positive TC) is unclear.
What alternative approach has the EAG suggested?	None. The EAG is not aware of any: • methods that could be used to generate robust evidence of comparative efficacy for systemic therapy-naïve patients with *RET* fusion-positive TC • comparator data for systemic therapy-naïve patients with *RET* fusion-positive TC. Therefore, the EAG is not able to suggest any alternative approaches.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice to assess the impact of *RET* fusion-positive status and line of treatment on clinical effectiveness results.

BSC=best supportive care; EAG=External Assessment Group; NICE=National Institute for Health and Clinical Excellence; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Issue 4 Uncertainty around selpercatinib safety evidence

Report section	Section 2.4, Section 2.5.2, Section 3.9 and Section 3.14
Description of issue and why the EAG has identified it as important	***RET*-mutant MTC** Selpercatinib has a conditional marketing authorisation for untreated *RET*-mutant MTC; further efficacy and safety information has been requested by the regulators. Selpercatinib (and cabozantinib/vandetanib) safety evidence is available from the LIBRETTO-531 trial for cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC. Frequencies of general and specific types of AEs (for example, treatment emergent Grade ≥3 AEs, SAEs and the incidence of fatigue) were often lower in the LIBRETTO-531 trial than in the LIBRETTO-001 trial. Focusing on LIBRETTO-001 trial any-line patient safety data may therefore over-estimate safety concerns for systemic therapy-naïve patients. ***RET* fusion-positive TC** Safety evidence for patients with *RET* fusion-positive TC is limited to selpercatinib and is only available for the any-line population (n=66).
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice to assess the relationship between line of treatment and incidence of adverse events.

AE=adverse event; EAG=External Assessment Group; MTC=medullary thyroid cancer; *RET*=rearranged during transfection; SAE=serious adverse event; TC=thyroid cancer originating in the follicular cells

1.5 *The cost effectiveness evidence: summary of the EAG's key issues*

Issue 5 *RET*-mutant MTC and *RET* fusion-positive TC populations: selpercatinib overall survival estimates

Report section	Section 6.2.1 and Section 6.2.2
Description of issue and why the EAG has identified it as important	The company selpercatinib OS estimates did not match company clinician 10-year and 20-year estimates. This issue was raised in the clarification letter (clarification question B1). In response to clarification, the company applied an adjustment factor at 5 years so that OS estimates were more closely aligned with clinical expert 10-year and 20-year estimates than with the estimates generated by the unadjusted distribution.
What alternative approach has the EAG suggested?	The EAG has generated exploratory cost effectiveness results using pessimistic and optimistic adjustment factors to provide an indication of the impact of the uncertainty around the 10-year and 20-year survival estimates suggested by company clinical experts.
What is the expected effect on the cost effectiveness estimates?	***RET*-mutant MTC (selpercatinib versus cabozantinib)** EAG pessimistic adjustment factor: **increases** company base case ICER per QALY gained by £6,841. EAG optimistic adjustment factor: **decreases** company base case ICER per QALY gained by £2,666. ***RET* fusion-positive TC (selpercatinib versus lenvatinib)** EAG pessimistic adjustment factor: **increases** company base case ICER per QALY gained by £9,734. EAG optimistic adjustment factor: **decreases** company base case ICER per QALY gained by £4,108.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice to identify the most appropriate approach to generating OS estimates for patients treated with selpercatinib may be helpful.

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; MTC=medullary thyroid cancer; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Issue 6 *RET*-mutant MTC population: cabozantinib overall survival estimates

Report section	Section 6.2.1
Description of issue and why the EAG has identified it as important	The company generated cabozantinib OS estimates by applying the EXAM trial HR to the stratified Weibull distribution (applied to EXAM trial placebo arm data) that was used to generate BSC OS estimates.
What alternative approach has the EAG suggested?	The EAG considers that OS estimates that are closer to company clinical expert 10-year OS estimates can be generated by applying the EXAM trial HR to spline 1 knot distribution fitted to EXAM trial placebo arm (BSC) data.
What is the expected effect on the cost effectiveness estimates?	EAG preferred distribution: **increases** the company base case ICER per QALY gained by £6,953.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice to identify the most appropriate approach to generating OS estimates for patients treated with cabozantinib may be helpful.

BSC=best supportive care; EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; OS=overall survival; MTC=medullary thyroid cancer; QALY=quality adjusted life year; *RET*=rearranged during transfection

Issue 7 Cabozantinib and lenvatinib drug costs: use of RDI rather than adherence data

Report section	Section 6.4
Description of issue and why the EAG has identified it as important	The company applied RDI multipliers to doses of cabozantinib and lenvatinib. As the lenvatinib and cabozantinib pack prices are the same regardless of dose size, dose adherence data should have been used to calculate treatment costs instead of RDI. When discussing cabozantinib, the NICE TA928[1] AC preferred adherence data to RDI data.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Cabozantinib adherence data may be available from the LIBRETTO-531 trial.

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; RDI=relative dose intensity

Issue 8 *RET*-mutant MTC and *RET* fusion-positive TC populations: health state utility values

Report section	Section 6.5
Description of issue and why the EAG has identified it as important	The company progression-free health state utility value appears quite high (0.8) as they are close to the population norm. The company progressed-disease health state value (0.5) appears implausibly low, particularly as clinical advice to the EAG is that patient health-related quality of life usually only deteriorates during the last 6 months of life and all patients spend more than 2 years in the progressed disease health state regardless of treatment.
What alternative approach has the EAG suggested?	Alternative health state utility values based on LIBRETTO-001 trial EORTC-QLQC-C30 data collected from the any-line *RET* fusion-positive TC population, whilst not without limitations, appear more plausible: Progression-free health state: [redacted] Progressed disease health state: [redacted]
What is the expected effect on the cost effectiveness estimates?	Selpercatinib versus cabozantinib: **increases** the company base case ICER per QALY gained by £5,593 Selpercatinib versus lenvatinib: **decreases** the company base case ICER per QALY gained by £1,199
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion.

EAG=External Assessment Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

1.6 *Summary of EAG's preferred assumptions and resulting ICER per QALY gained*

Table D *RET*-mutant MTC population: selpercatinib versus cabozantinib (deterministic results, selpercatinib PAS price)

EAG revisions	Incremental		ICER	
	Costs	QALYs (x1.2 modifier where relevant)	£/QALY (x1.2 modifier where relevant)	Change from company base case
A. Company clarification base case	[redacted]	[redacted]	**£29,713***	-
R1) Stratified spline 1 knot distribution to extrapolate cabozantinib OS	[redacted]	[redacted]	£36,666	£6,953
R2) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£35,306	£5,593
R3) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£36,554*	£6,841
R4) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£27,047*	-£2,666
B. EAG alternative scenario (R1-R2)	[redacted]	[redacted]	**£36,791**	**£7,078**
C. EAG exploratory scenarios				
C1. R1-R3	[redacted]	[redacted]	**£49,853**	**£20,141**
C2. R1-R2, R4	[redacted]	[redacted]	**£31,997**	**£2,284**

*1.2x severity modifier applied
EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER=incremental cost-effectiveness ratio; MTC=medullary thyroid cancer; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table E *RET*-mutant MTC population: selpercatinib versus BSC (deterministic results, selpercatinib PAS price)

EAG revisions	Incremental		ICER	
	Costs	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from company base case
A. Company clarification revised base case	[redacted]	[redacted]	**£39,481**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£39,689	£209
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£47,376	£7,895
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£36,260	-£3,220
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£39,689**	**£209**
C. EAG exploratory scenarios				
C1. R1-R2	[redacted]	[redacted]	**£51,150**	**£11,669**
C2. R1, R3	[redacted]	[redacted]	**£35,141**	**-£4,340**

BSC=best supportive care; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table F *RET* fusion-positive TC population: selpercatinib versus lenvatinib (deterministic results, selpercatinib PAS price)

EAG revisions	Incremental		ICER	
	Costs	QALYs	£/QALY	Change from company base case
A. Company clarification revised base case*	[redacted]	[redacted]	**£36,329**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£35,130	-£1,199
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£46,063	£9,734
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£32,221	-£4,108
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£35,130**	**-£1,199**
C. EAG exploratory scenarios				
C1. (R1-R2)	[redacted]	[redacted]	**£50,131**	**£13,802**
C2. (R1, R3)	[redacted]	[redacted]	**£29,756**	**-£6,573**

EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; OS=overall survival; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table G *RET* fusion-positive TC population: selpercatinib versus BSC (deterministic results, selpercatinib PAS price)

EAG revisions	Incremental		ICER	
	Costs	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from company base case
A. Company clarification base case	[redacted]	[redacted]	**£37,050**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£36,312	-£738
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£43,021	£5,971
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£34,138	-£2,912
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£36,312**	**-£738**
C. EAG exploratory scenarios				
C1. R1-R2	[redacted]	[redacted]	**£45,285**	**£8,235**
C2. R1, R3	[redacted]	[redacted]	**£32,368**	**-£4,681**

BSC=best supportive care; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; OS=overall survival; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Modelling errors identified and corrected by the EAG are described in Section 6.1 to Section 6.6. Results from exploratory and sensitivity analyses carried out by the EAG are provided in Section 6.7.

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

This appraisal focuses on selpercatinib (brand name: Retsevmo) as a treatment option for patients with untreated advanced thyroid cancer with rearranged during transfection (*RET*) alterations.

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company during the clarification stage. In line with the CS, in this EAG report, thyroid cancer subtypes that develop in follicular cells are referred to as 'TC'; medullary thyroid cancer (MTC) and TC are collectively referred to as thyroid cancer.

2.2 *Background*

2.2.1 Thyroid cancer

Thyroid cancer is rare and accounts for approximately 1% of new UK cancer cases.[2] It is more commonly diagnosed in women than men.[2] The main thyroid cancer histological subtypes are: papillary, follicular, Hürthle cell, poorly differentiated, undifferentiated (also known as anaplastic) thyroid cancer and MTC (Table 1).

Table 1 Histological subtypes of thyroid cancer

Histological thyroid cancer subtype			Proportion of all thyroid cancer cases	Prevalence of *RET* alterations
Thyroid cancer originating in the follicular cells	Differentiated	Papillary	90%	5 to 40%
		Follicular	4%	Uncommon
		Hürthle cell	2%	Uncommon
	Poorly differentiated		3 to 5%	4 to 6%
	Undifferentiated	Anaplastic	<1%	Uncommon
Thyroid cancer originating in the non-follicular cells		Medullary	4%	55 to 62.5%[a]

[a] 100% of hereditary MTC (hereditary MTC accounts for 25% of all MTC cases); 40% to 50% sporadic MTC (sporadic MTC accounts for 75% of all MTC cases)
CS=company submission; MTC=medullary thyroid cancer
Source: CS, pp20-21 and Figure 1; Tong 2022[3]

Papillary, follicular, Hürthle cell, poorly differentiated and undifferentiated thyroid cancer develop from follicular cells. Papillary, follicular and Hürthle cell thyroid cancer are classified as differentiated thyroid cancers and are typically curable; the 10-year survival rate for patients with differentiated TC is 84.3%.[2] Undifferentiated thyroid cancer is typically more aggressive than other subtypes. In the UK and Ireland, the 5-year survival rate for patients with undifferentiated TC is 6%.[4]

MTC develops from non-follicular cells; patients with MTC have a poorer prognosis than patients with differentiated TC.[5] The 10-year survival rates for women and men with MTC are 82% and 61%, respectively.[4] The 5-year survival rates for women and men with MTC in the UK and Ireland are 76% and 68%, respectively.[4] MTC can be sporadic (75% of all MTC cases) or hereditary (25% of all MTC cases).[6]

2.2.2 Thyroid cancer with *RET* alterations

The RET protein is a transmembrane receptor tyrosine kinase that is expressed by multiple tissue types, including lung, adrenal medulla and thyroid.[7] In healthy people, RET protein is involved in cell growth, cell division and cell differentiation.[8] Abnormal activity of RET protein in cancer is caused by mutations and fusions to the *RET* gene encoding RET protein.[8]

RET alterations have been detected in thyroid cancers and are most prevalent in papillary TC and MTC. Almost all cases (approximately 100%) of hereditary MTC and around 40% to 50% of sporadic MTC cases test positive for *RET* mutations.[9] For patients with hereditary MTC, the most common *RET* mutation is MEN2A which accounts for 80% of hereditary MTC cases.[10] The M918T *RET* mutation is rare in hereditary MTC (accounting for approximately 5% of hereditary MTC cases) but is the most common somatic mutation in sporadic MTC tumours (up to 40% of sporadic MTC cases).[10] The M918T *RET* mutation is associated with early onset and aggressive disease.[11] Survival data from a cohort study[12] of 100 patients with sporadic MTC (mean follow-up: 10.2 years) showed that patients with *RET*-mutant MTC had statistically significantly worse overall survival (OS) than patients with MTC without *RET* mutations (p=0.006).

For papillary TC, the prevalence of *RET* fusions ranges from 5% to 20%; however, some smaller prevalence studies have reported *RET* fusion rates of up to 40%.[11,13] For patients with *RET* fusion-positive papillary TC, the most common *RET* fusions are *RET/PTC1* (*RET* and *CCDC6* fusion) and *RET/PTC3* (*RET* and *NCOA4* fusion); these account for 60% and 20% of *RET* fusion-positive papillary TC cases, respectively.[9] There is no consensus about whether patients with *RET* fusion-positive TC have a worse prognosis than patients with TC without *RET* fusions.[14-17]

2.3 *Company's overview of current service provision*

The company has presented the current NHS treatment pathways. The company has also presented the anticipated NHS treatment pathways should selpercatinib be recommended by the National Institute for Health and Care Excellence (NICE) for treating:

- patients with advanced *RET*-mutant MTC (CS, Figure 4)
- patients with advanced *RET* fusion-positive TC (CS, Figure 5)

The company's pathways were informed by the NICE thyroid cancer assessment and management guidelines (NG230),[18] the UK national multidisciplinary thyroid cancer management guidelines[19] and the British Thyroid Association thyroid cancer management guidelines.[20]

2.3.1 Treatment pathway for patients with advanced *RET*-mutant MTC

In current NHS clinical practice, patients with advanced *RET*-mutant MTC will typically undergo a partial or full thyroidectomy after diagnosis and staging, while patients with disease that is unsuitable for surgery may receive radiotherapy to manage local symptoms.[19]

In March 2018, NICE recommended cabozantinib as a treatment option for adult patients with unresectable, locally advanced or metastatic MTC (TA516)[21] and in December 2018, NICE recommended that vandetanib should *not* be a treatment option for adult patients with unresectable, locally advanced or metastatic MTC (TA550).[22] Cabozantinib is, therefore, the only systemic treatment currently routinely available to adult NHS patients with advanced MTC. Clinical advice to the company[23] was that 80% to 90% of patients with advanced *RET*-mutant MTC receive cabozantinib; clinical advice to the EAG agrees with the advice given to the company. In addition, clinical advice to the EAG is that, due to poor Eastern Cooperative Oncology Group performance status (ECOG PS) and comorbidities, cabozantinib is not suitable for approximately 10% of patients with MTC and these patients receive best supportive care (BSC), which comprises monitoring, palliative radiotherapy and palliative care.

In current NHS clinical practice, there are no routinely available NICE recommended treatment options for patients with advanced MTC aged 12 to 18 years.

2.3.2 Treatment pathway for patients with advanced *RET* fusion-positive TC

In current NHS clinical practice, the treatment pathway for patients with advanced *RET* fusion-positive TC is separated into two, (i) patients with differentiated *RET* fusion-positive TC and (ii) patients with undifferentiated *RET* fusion-positive TC.

In current NHS clinical practice, patients with advanced *RET* fusion-positive differentiated TC typically undergo a partial or full thyroidectomy, while patients who are unsuitable for surgery typically receive radiotherapy to manage local symptoms.[19] Clinical advice to the EAG is that following partial or full thyroidectomy, all patients with advanced *RET* fusion-positive differentiated TC receive radioactive iodine therapy.

Approximately 5% to 15% of patients with differentiated TC develop radioactive iodine refractory disease.[24] In August 2018, NICE recommended lenvatinib and sorafenib as

treatment options for adult patients with advanced differentiated TC whose disease does not respond to radioactive iodine if they have not previously had a tyrosine kinase inhibitor (TKI) or they have had to stop taking a TKI within 3 months of starting it due to toxicity.[25] In current NHS clinical practice, lenvatinib and sorafenib are the only NICE recommended treatments routinely available for adult patients with differentiated TC whose disease is radioactive iodine therapy refractory. In November 2023, NICE recommended that cabozantinib should *not* be a treatment option for adult patients with locally advanced or metastatic differentiated TC that is unsuitable for, or refractory to, radioactive iodine, and whose disease has progressed after systemic treatment (i.e., lenvatinib or sorafenib) (TA928).[1]

Clinical advice to the company is that 90% to 95% of adult patients with radioactive iodine therapy-refractory differentiated TC who receive an MKI are treated with lenvatinib or sorafenib; however, sorafenib is rarely used. Clinical advice to the EAG is that approximately 80% of adult patients with radioactive iodine therapy-refractory differentiated TC are treated with lenvatinib or sorafenib (<5%) and that the remaining patients receive BSC. In current NHS clinical practice, there are no routinely available NICE recommended treatment options for patients with advanced undifferentiated TC or for patients with advanced TC aged 12 to 18 years.

2.4 *Selpercatinib*

Selpercatinib is a selective kinase inhibitor,[26] it is the first kinase inhibitor to selectively target the RET tyrosine kinase receptor. Selpercatinib prevents the activation of fusion, mutant and wild type isoforms of RET and disrupts the signalling pathway to stop tumour cell survival, proliferation, migration and angiogenesis (CS, Table 2).

Selpercatinib is administered orally and is available as 40mg and 80mg hard capsules. The recommended dose is 120mg twice daily (BID) for patients who weigh <50kg and 160mg BID for patients who weigh ≥50kg and, for patients experiencing some adverse effects, it is recommended that the dose is interrupted and/or reduced.[27]

Selpercatinib has a conditional licence from the European Medicines Agency (EMA)[27,28] and from the Medicines and Healthcare products Regulatory Agency (MHRA)[26] for (i) the treatment of patients with advanced MTC and TC with *RET* alterations who have received prior MKI-treatment and (ii) for systemic therapy-naïve patients with *RET*-mutant MTC. Selpercatinib is not yet licensed as a treatment option for patients with *RET* fusion-positive TC who are systemic therapy-naïve. Relevant selpercatinib marketing authorisations are presented in Table 2.

Table 2 Selpercatinib marketing authorisations relevant to this appraisal

Regulatory body	Date	Indication
Conditional marketing authorisation		
EMA	February 2021[28]	Patients aged ≥12 years with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib Adult patients with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with sorafenib and/or lenvatinib
MHRA	February 2021[26]	
EMA	September 2022[27]	Patients aged ≥12 years with advanced *RET*-mutant MTC
MHRA	February 2023[26]	
Conditional marketing authorisation application		
EMA[a]	September 2022	Patients with *RET* fusion-positive TC who are systemic therapy-naïve[c]
MHRA[b]	[redacted]	

[a] A positive opinion from the CHMP ([redacted]) has not yet been published
[b] MHRA approval under a conditional marketing authorisation is expected in [redacted]
[c] The anticipated future licensed indication is selpercatinib "[redacted]".
CHMP=Committee for Medicinal Products for Human Use; CS=company submission; EMA=European Medicines Agency; MHRA=Medicines and Healthcare products Regulatory Agency; MTC=medullary thyroid cancer; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 2

In November 2021, NICE recommended selpercatinib for use within the Cancer Drugs Fund (CDF) as an option for treating advanced MTC and TC with *RET* alterations after prior systemic treatment (TA742).[29] As highlighted in Section 2.3.2 of this report, there are no routinely available NICE recommended treatment options for patients with undifferentiated TC and, therefore, within the NICE recommendation, patients with undifferentiated TC are eligible to receive selpercatinib via the CDF regardless of whether they have or have not received prior systemic therapy, if the conditions set out in the Managed Access Agreement[30] are followed.

2.4.1 Company proposed position for selpercatinib in NHS treatment pathways

In the current appraisal, the company has positioned (CS, Figure 4 and Figure 5) selpercatinib as:

- an alternative treatment to cabozantinib and BSC for patients aged ≥12 years with advanced *RET*-mutant MTC who require systemic therapy and have not previously received or are ineligible for systemic therapy with cabozantinib following partial or full thyroidectomy or radiotherapy (CS, Figure 4).
- an alternative treatment to lenvatinib, sorafenib and BSC for patients aged ≥12 years with advanced *RET* fusion-positive differentiated TC whose disease is radioactive iodine therapy refractory and who require systemic therapy and have not previously received systemic therapy following partial or full thyroidectomy (CS, Figure 5).
- an active treatment option as an alternative to BSC for patients with undifferentiated TC following full thyroidectomy or for patients with undifferentiated TC whose disease is not fully resectable (CS, Figure 5).

2.5 *Critique of company's definition of the decision problem*

The company has presented clinical and cost effectiveness evidence for selpercatinib as a treatment option for systemic therapy-naïve patients with advanced *RET*-mutant MTC and for systemic therapy-naive patients with advanced *RET* fusion-positive TC.

The primary source of direct selpercatinib clinical effectiveness evidence presented by the company is the LIBRETTO-001 trial.[31] The company has also provided direct clinical effectiveness evidence for the comparison of selpercatinib versus cabozantinib from the LIBRETTO-531 trial.[32] Key LIBRETTO-001 and LIBRETTO-531 trial characteristics are presented in Table 3.

Table 3 Key characteristics of the LIBRETTO-001 and LIBRETTO-531 trials

Trial	Study design	Start date	Intervention	Comparator	Population(s) relevant to this appraisal
LIBRETTO -001	On-going, multi-centre, open-label, phase I/II single arm basket trial	May 2017[a]	Selpercatinib (N=837)[b]	n/a	• Cabozantinib/vandetanib-naïve patients with advanced *RET*-mutant MTC (n=143) • Any-line patients with advanced *RET*-mutant MTC (n=295) • Systemic therapy-naïve patients with advanced *RET* fusion-positive TC (n=24) • Any-line patients with advanced *RET* fusion-positive TC (n=65)
LIBRETTO -531	On-going, multi-centre, open-label, phase III RCT	Feb 2020[c]	Selpercatinib (n=193)	Cabozantinib (n=73) or vandetanib (n=25)[d]	Cabozantinib/vandetanib-naïve patients with advanced *RET*-mutant MTC

[a] Latest LIBRETTO-001 trial DCO available: 13 January 2023
[b] The overall LIBRETTO-001 trial population includes patients with *RET* fusion-positive NSCLC, pancreatic cancer and colorectal cancer as well as patients with other agnostic tumours with *RET* activation
[c] Latest LIBRETTO-531 trial DCO available: 22 May 2023 (interim analysis)
[d] In the LIBRETTO-531 trial, 73 patients and 25 patients were randomised to receive cabozantinib and vandetanib, respectively (ITT population). However, due to supply issues, the actual number of patients who received cabozantinib and vandetanib was n=71 and n=27, respectively (subgroup efficacy analyses populations).
CS=company submission; DCO=data cut-off; ITT=intention-to-treat; MTC=medullary thyroid cancer; n/a=not applicable; NSCLC=non-small cell lung cancer; RCT=randomised controlled trial; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 6, Table 7 and Table 9; CS, Appendix M, Table 62; Hadoux 2023[32]

The company used evidence from indirect treatment comparisons (ITCs) to inform clinical and cost effectiveness analyses of selpercatinib versus relevant comparators. Data from systemic therapy-naïve and systemic therapy-experienced (i.e., any-line) patients with and without *RET* alterations were used to inform the company ITCs.

A summary of the decision problem outlined in the final scope[33] issued by NICE and addressed by the company is presented in Table 4. More information regarding the key issues relating to the decision problem is provided in Sections 2.5.1 to 2.5.5.

Table 4 Summary of final scope issued by NICE, decision problem addressed by the company and EAG comments

Parameter	Final scope issued by NICE	Decision problem addressed by the company with rationale	EAG comments
Population	***RET*-mutant MTC** Adults and adolescents 12 years and older with untreated advanced *RET*-mutant MTC who require systemic therapy	***RET*-mutant MTC** Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy (and who have not previously received systemic therapy)	***RET*-mutant MTC** In the LIBRETTO-001 and LIBRETTO-531 trials, cabozantinib/vandetanib-naïve (also referred to as systemic therapy-naïve) patients with *RET*-mutant MTC were considered by the company to reflect NHS patients with untreated, advanced *RET*-mutant MTC For patients with *RET*-mutant MTC, the company provided clinical effectiveness evidence for the i) cabozantinib/vandetanib-naïve population and the ii) any-line population; cost effectiveness evidence was generated using data from any-line populations
	***RET* fusion-positive TC** Adults with untreated advanced *RET* fusion-positive thyroid cancer who require systemic therapy	***RET* fusion-positive TC** Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy (and who have not previously received systemic therapy)	***RET* fusion-positive TC** In the LIBRETTO-001 trial, systemic therapy-naïve patients with *RET* fusion-positive TC (including patients who had received prior radioactive iodine therapy) were considered by the company to reflect NHS patients with untreated, advanced *RET* fusion-positive TC For patients with *RET* fusion-positive TC, the company provided clinical effectiveness evidence for the i) systemic therapy-naïve and the ii) any-line population; cost effectiveness evidence was generated using data from any-line populations
Intervention	Selpercatinib	Selpercatinib	As per scope
Comparator(s)	***RET*-mutant MTC** • cabozantinib (adults only) • BSC	***RET*-mutant MTC** • cabozantinib • BSC In line with the NICE final scope. In this submission, cabozantinib is positioned as the primary comparator in the MTC indication. Clinical expert opinion gained to	***RET*-mutant MTC** As per scope. The EAG agrees with the company that cabozantinib is the main comparator for patients with *RET*-mutant MTC. BSC is a treatment option for patients for whom cabozantinib is not a treatment option

Parameter	Final scope issued by NICE	Decision problem addressed by the company with rationale	EAG comments
		validate the MTC treatment pathway in the UK estimated that 85-95% of individuals with advanced *RET*-mutant MTC in the UK will receive treatment with cabozantinib[23] BSC is positioned as a secondary comparator in this submission in the MTC indication. BSC is only received by patients who are ineligible for treatment with cabozantinib, including patients who may be unable to tolerate the associated toxicity profile and children and adolescents aged 12-17 years	
	***RET* fusion-positive TC** • lenvatinib • sorafenib • BSC	***RET* fusion-positive TC** • lenvatinib • sorafenib • BSC In this submission, lenvatinib is positioned as the primary comparator in the TC indication, of most relevance to decision making. Clinical expert opinion obtained to support the development of this submission confirmed that lenvatinib is the predominant MKI used in UK clinical practice, due to a perceived improved efficacy and similar AE profile with respect to sorafenib.[23] UK clinical experts indicated for patients receiving MKIs, the vast majority (90%-95%) of patients receive lenvatinib.[23] UK clinical experts stated that sorafenib is rarely used, when compared with lenvatinib, so sorafenib is not considered a relevant comparator in this appraisal BSC is positioned as secondary comparators in this submission. BSC is only received by patients ineligible for treatment with an MKI, including children and adolescents aged 12-17 years. Clinical expert opinion indicates that 90-95% of patients in the TC indication would receive a MKI[23]	***RET* fusion-positive TC** The EAG agrees with the company that lenvatinib is the main comparator for patients with differentiated *RET* fusion-positive TC. Clinical advice to the EAG is that <5% of NHS patients with radioactive iodine therapy-refractory differentiated TC are treated with sorafenib. BSC is a treatment option for patients for whom lenvatinib or sorafenib are not treatment options

Parameter	Final scope issued by NICE	Decision problem addressed by the company with rationale	EAG comments
Outcomes	• OS • PFS • Response rate • AEs of treatment • HRQoL	**Primary endpoints** • BOR[a] and ORR **Key secondary endpoints** • DoR • Time to response and time to best response • CBR • OS • PFS • AEs • HRQoL	All outcomes specified in the final scope issued by NICE are LIBRETTO-001 trial and/or LIBRETTO-531 primary or secondary endpoints
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out 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 PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account The use of selpercatinib is conditional on the	These details were provided in response to Clarification Question C5 (Table 18) The economic analysis has been provided in line with the NICE reference case **Outcomes** The ICER of selpercatinib versus each comparator was evaluated in terms of an incremental cost per QALY gained (CS, p141) **Model time horizon** 25 years in base case **Model perspective** The analysis was conducted from the perspective of the NHS and Personal Social Services (CS, p13) **Commercial arrangements** A confidential Patient Access Scheme of [redacted] has been provided alongside this submission. The commercial arrangements for comparators in this submission are not known **Diagnostic testing for *RET* fusions** The cost of *RET* testing has been included in	The company has provided cost effectiveness estimates in terms of the incremental cost per quality adjusted life year gained for patients with RET-mutant MTC and patients with RET fusion-positive TC. Post-clarification, outcomes were assessed over a 35 year time horizons and costs were considered from an NHS and PSS perspective

Parameter	Final scope issued by NICE	Decision problem addressed by the company with rationale	EAG comments
	presence of *RET* mutation or fusion. The economic modelling should include the costs associated with diagnostic testing for *RET* mutation or 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	the base case of the economic model, in line with TA911.[34] Exclusion of *RET* testing was not considered as a scenario analysis The model base case is in line with the NICE final scope No scenario analyses for *RET* testing were conducted, as excluding costs of *RET* testing is anticipated to have minimal impact on cost-effectiveness results	
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	*(Clarification Question C5, Table 18)* In line with the NICE final scope	As per scope

[a] In the CS, Table 1, BOR was listed as a primary endpoint however only ORR was listed as a primary endpoint in the LIBRETTO-001 TSAP[35]
AE=adverse event; BOR=best overall response; BSC=best supportive care; CBR=clinical benefit rate; CS=company submission; DoR=duration of response; EAG=External Assessment Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; ITC=indirect treatment comparison; MKI=multikinase inhibitor; MTC=medullary thyroid cancer; NGS=next generation sequencing; NICE=National Institute for Health and Care Excellence; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells; TSAP=trial statistical analysis plan
Source: CS, Table 1

2.5.1 Population

Direct evidence: *RET*-mutant MTC

Some LIBRETTO-001 trial patients with *RET*-mutant MTC and all LIBRETTO-531 trial patients were cabozantinib/vandetanib-naïve. Clinical advice to the company[23] and to the EAG is that these patients are representative of NHS patients with untreated advanced *RET*-mutant MTC. In the LIBRETTO-001 trial, [redacted]/143 ([redacted]) patients with *RET*-mutant MTC who were considered to be cabozantinib/vandetanib-naïve had received other prior systemic therapy (nine of these patients had received a prior MKI). Clinical advice to the EAG is that patients with MTC only receive systemic therapy with MKIs for advanced disease and, therefore, patients who had received prior MKIs (e.g., cabozantinib, lenvatinib, sorafenib) for advanced disease should be considered systemic therapy-experienced. The LIBRETTO-001 and LIBRETTO-531 trials include very few patients with *RET*-mutant MTC who are aged between 12 and 18 years (n=[redacted] and n=1, respectively).

Direct evidence: *RET* fusion-positive TC

Clinical effectiveness evidence for selpercatinib as a treatment option for systemic therapy-naive patients with advanced *RET* fusion-positive TC is only available from a small proportion of the LIBRETTO-001 trial population (systemic therapy-naive patients with *RET* fusion-positive TC: n=24; any-line patients with *RET* fusion-positive TC: n=65). Clinical advice to the company[23] and to the EAG is that these patients are representative of NHS patients with untreated advanced *RET* fusion-positive TC.

In the LIBRETTO-001 trial, most patients in the systemic therapy-naïve (n=[redacted]/24) and any-line populations (n=[redacted]/65) had *RET* fusion-positive papillary TC; [redacted]/65 any-line patients had *RET* fusion-positive undifferentiated TC. Patients with *RET* fusion-positive undifferentiated TC are eligible to receive selpercatinib via the CDF, regardless of whether they have or have not received prior systemic therapy if the conditions set out in the TA742 Managed Access Agreement[30] are followed.

For patients with *RET* fusion-positive TC, the population specified in the company decision problem includes adolescents aged 12 to 18 years, i.e., is broader than the *RET* fusion-positive TC population (adults only) specified in the final scope issued by NICE. The LIBRETTO-001 trial did not include any patients with *RET* fusion-positive TC aged 12 to 18 years. Clinical advice to the EAG is that patients aged 12 to 18 years who have thyroid cancer with *RET* alterations are expected to have the same clinical response to systemic therapies as patients aged ≥18 years.

Some LIBRETTO-001 trial patients with *RET* fusion-positive TC ([redacted]/24; [redacted]) who were considered to be systemic therapy-naïve had received prior radioactive iodine therapy. Clinical advice to the EAG is that patients who have received radioactive iodine therapy are appropriately considered to be systemic therapy-naïve.

Indirect evidence

The company carried out:

- *RET*-mutant MTC: unanchored matching-adjusted indirect comparisons (MAICs) were carried using data from any-line patients with *RET*-mutant MTC (LIBRETTO-001 trial and EXAM trial[36] data) to compare selpercatinib versus cabozantinib and versus BSC
- *RET* fusion-positive TC: naïve, unadjusted indirect treatment comparisons were carried out to compare selpercatinib versus lenvatinib, versus sorafenib and versus BSC using the following data:
    - LIBRETTO-001 trial*: RET* fusion-positive TC any-line patients (selpercatinib)
    - SELECT trial:[37] unknown *RET* fusion status TC any-line patients (lenvatinib and BSC)
    - DECISION trial:[38] unknown *RET* fusion status TC systemic therapy-naïve patients (sorafenib).

The LIBRETTO-001 and EXAM trials included systemic therapy-naïve and systemic therapy-experienced patients. As clinical effectiveness results from the EXAM trial were only reported for the any-line population, LIBRETTO-001 trial any-line MTC population data were used in the indirect comparisons.

The proportion of EXAM trial placebo arm *RET*-mutant MTC patients and the proportions of SELECT trial and DECISION trial *RET* fusion-positive TC patients are unknown. Patients with *RET*-mutant MTC have a worse prognosis than patients with MTC without *RET* mutations (Section 2.2.2); however, there is no consensus about whether patients with *RET* fusion-positive TC have a worse prognosis than patients with TC without *RET* fusions.

2.5.2 Intervention

The company has presented evidence for selpercatinib as per its conditionally licensed EMA[27,28] and MHRA[26] indications for cabozantinib/vandetanib-naïve patients with advanced *RET*-mutant MTC, and as per the anticipated positive EMA Committee for Medicinal Products for Human Use (CHMP) and proposed MHRA licensed indication for systemic therapy-naïve patients with advanced *RET* fusion-positive TC (CS, Table 2).

The EMA approved a conditional marketing authorisation for selpercatinib based on LIBRETTO-001 trial data. In the European Public Assessment Report (EPAR),[27] it is stated that to fulfil the conditional marketing authorisation, the company must provide:

- the final LIBRETTO-001 trial clinical study report (CSR) by 31 December 2023 to confirm the clinical effectiveness of selpercatinib for *RET*-mutant MTC and *RET* fusion-positive thyroid cancer
- and the LIBRETTO-531 trial CSR by 30 September 2025 to confirm the clinical effectiveness of selpercatinib for *RET*-mutant MTC.

2.5.3 Comparators

Systemic therapy-naïve patients with *RET*-mutant MTC

The company considers (and clinical advice to the EAG agrees) that cabozantinib is the main comparator for patients with *RET*-mutant MTC. Clinical advice to the EAG is that cabozantinib is unsuitable and/or unacceptable for approximately 10% of patients with *RET*-mutant MTC and that these patients receive BSC (see Section 2.3.1).

The company presented direct evidence for the comparison of selpercatinib versus cabozantinib for cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC from the LIBRETTO-531 trial. The company also carried out MAICs to provide indirect evidence for the comparison of selpercatinib versus cabozantinib using data from any-line patients with *RET*-mutant MTC from the LIBRETTO-001 trial and the EXAM trial. The EAG considers that the LIBRETTO-531 trial provides the best available clinical effectiveness evidence for the comparison of selpercatinib versus cabozantinib as:

- all patients are cabozantinib/vandetanib-naïve
- the trial provides direct evidence for the most relevant comparator, i.e., cabozantinib.

The EAG acknowledges, however, that the LIBRETTO-531 trial has a substantially shorter follow-up than the LIBRETTO-001 trial (LIBRETTO 531 trial interim analysis, selpercatinib arm median PFS follow-up=[redacted] months; LIBRETTO-001 trial median PFS follow-up=[redacted] months).

The company carried out MAICs to provide indirect evidence for the comparison of selpercatinib versus BSC using data from any-line patients with *RET*-mutant MTC from the LIBRETTO-001 trial and data from any-line patients with any *RET* mutation status MTC from the EXAM trial placebo arm. The company considered that the EXAM trial placebo arm PFS and OS data could be used as proxies for BSC data; clinical advice to the EAG is that this was reasonable for PFS but not for OS as, in the EXAM trial, 49.5% of placebo arm patients subsequently received systemic therapies. Patients treated with BSC in NHS clinical practice would be unlikely to receive systemic therapies on disease progression.

In the EXAM trial, patients who received placebo were eligible and suitable to receive cabozantinib. Therefore, the placebo arm population is representative of NHS patients for whom cabozantinib is suitable but who are not treated with cabozantinib and instead receive BSC.

Systemic therapy-naïve patients with *RET* fusion-positive TC

The company considers (and clinical advice to the EAG agrees) that lenvatinib is the main comparator for patients with *RET* fusion-positive TC. Clinical advice to the EAG agrees with the company and highlights that sorafenib is also a relevant comparator for patients with *RET* fusion-positive TC but is only used to treat <5% of NHS patients.

The company carried out naïve, unadjusted indirect treatment comparisons to provide evidence for the comparison of selpercatinib versus lenvatinib and versus sorafenib using data from:

- any-line patients with *RET* fusion-positive TC from the LIBRETTO-001 trial (selpercatinib)
- any-line patients with unknown *RET* fusion status from the SELECT trial (lenvatinib)
- systemic therapy-naïve patients with unknown *RET* fusion status from the DECISION trial (sorafenib; all patients in the DECISION trial were systemic therapy-naïve).

The company presented indirect evidence for the comparison of selpercatinib versus BSC using data from any-line patients with *RET* fusion-positive TC in the LIBRETTO-001 trial (selpercatinib) and patients with unknown *RET* fusion status in the SELECT trial (BSC). The company considered that SELECT trial placebo arm PFS and OS data and the DECISION trial placebo arm PFS data could also be used as proxies for BSC data. Clinical advice to the EAG is that this was reasonable for PFS but not for OS because patients in the SELECT and DECISION trial placebo arms were permitted to crossover to active treatment and/or receive other subsequent active treatments. Patients treated with BSC in NHS clinical practice would be unlikely to receive systemic therapies on disease progression. The EAG agrees with the company that SELECT trial placebo arm OS data may be a suitable proxy for BSC OS data as the company adjusted SELECT trial K-M OS curves to account for treatment crossover using the rank-preserving structural failure time (RPSFT) method.

In the SELECT and DECISION trials, patients who received placebo were eligible and suitable to receive lenvatinib or sorafenib, respectively. Therefore, the placebo arm populations are representative of NHS patients for whom lenvatinib or sorafenib are suitable but who are not treated with lenvatinib or sorafenib and instead receive BSC.

2.5.4 Outcomes

Clinical advice to the EAG is that the outcomes listed in the final scope issued by NICE are the most relevant outcomes for patients with *RET*-mutant MTC and *RET* fusion-positive TC. The LIBRETTO-001 trial primary endpoint is objective response rate (ORR) and the LIBRETTO-531 trial primary endpoint is progression-free survival (PFS). The company presented OS and PFS results from the LIBRETTO-001 and LIBRETTO-531 trials; however,

there are low numbers of OS and PFS events in the LIBRETTO-531 trial, therefore, LIBRETTO-531 trial survival results are uncertain.

The company provided indirect evidence for the comparison of selpercatinib versus cabozantinib, versus lenvatinib, versus sorafenib and versus BSC for the key outcomes, PFS and OS.

2.5.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 35-year time period (which the company considered was equivalent to a lifetime horizon) and costs were considered from an NHS and Personal and Social Services (PSS) perspective.

Selpercatinib is available to the NHS at a discounted Patient Access Scheme (PAS) price.

2.6 *Other considerations*

In November 2021, NICE[29] recommended selpercatinib for use within the CDF as a treatment for advanced *RET*-mutant MTC and *RET* fusion-positive TC after prior systemic treatment. The CDF recommendation was made due to the immaturity of LIBRETTO-001 trial data and consequent uncertainty around trial results. The company considered (CS, Section 3.8) that the evidence presented in the CS is sufficiently robust for NICE to make a recommendation for selpercatinib to be routinely commissioned by the NHS and stated that [redacted].

The company considered (CS, Section 1.4) that there may be inequality issues relating to patient access to *RET*-targeted treatments due to national variations in access to genetic testing. Clinical advice to the EAG is that patients with thyroid cancer are routinely tested for *RET* status in NHS clinical practice and that next generation sequencing (NGS) testing is routinely available, however, the wait time for NGS results can be up to 2 months.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company to support selpercatinib as a treatment option for patients with *RET*-mutant MTC and for patients with *RET* fusion-positive TC.

3.1 *Critique of the methods of review(s)*

The company conducted a systematic literature review (SLR) to identify sources of clinical effectiveness evidence. The company's SLR was designed to identify studies (not limited to randomised controlled trials [RCTs]) of selpercatinib and comparators as treatments for advanced or metastatic *RET*-mutant MTC and *RET* fusion-positive TC (CS, Section B.2.1 and Appendix D.1); full details of the methods used by the company are presented in the CS (Appendix D). The searches were comprehensive and updated 6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the EAG's in-house systematic review checklist is presented in Table 5. The EAG considers that the company's systematic review methods were appropriate.

Table 5 The EAG's appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of PICOS?	Yes	CS, Appendix D.1.2, Table 15
Were appropriate sources searched?	Yes	CS, Appendix D.1.1, p5
Was the timespan of the searches appropriate?	Yes	CS, Appendix D.1.1, p31
Were appropriate search terms used?	Yes	CS, Appendix D.1.1, Table 1 to Table 12
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1.2, Table 15 There were more "relevant comparators" for the SLR (as these could include "Any active systemic therapy") than are relevant to this appraisal
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.2, p32
Was data extracted by two or more reviewers independently?	Partial	CS, Appendix D.1.2 One reviewer extracted data and the data were then checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Appendix D.1.8, Table 22 and Appendix D3, Table 23 to Table 24. The company used the CASP[39] checklist for single-arm studies. For the RCTs, the company used the NICE process and methods [PMG6] methodology checklist for RCTs[40]
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D.1.2, p33
Were attempts to synthesise evidence appropriate?	Yes	MAICs/naïve indirect comparisons were performed. See Section 3.10.4, Section 3.10.6, Section 3.11.4 and Section 3.11.6 for a discussion of company methods and EAG's critique

CASP=Critical Appraisals Skills Programme; CS=company submission; EAG=External Assessment Group; MAIC=matching-adjusted indirect comparison; PICOS=population, interventions, comparators, outcomes and study designs; RCT=randomised controlled trials; SLR=systematic literature review
Source: LR*i*G in-house checklist

3.2 *Included trials*

The company stated that their SLR identified 90 publications of 24 unique studies (CS, p36, and CS Appendix D, Figure 1). However, only 18 studies are listed in the CS, Appendix D, Table 16, although a further six studies were included in the ITC feasibility assessments (CS, Appendix D, Table 17 and CS, Appendix D, Table 18).

Of the 24 unique studies, there were two single-arm trials of selpercatinib, the LIBRETTO-001 trial and LIBRETTO-321 trial (see Table 6 for references); the company only presented evidence from the LIBRETTO-001 trial in the CS. The EAG agrees that the LIBRETTO-321 trial provides less relevant and less robust evidence than the LIBRETTO-001 trial (due to its location [China], sample size [n=29 for RET-mutant MTC and n=1 for RET fusion-positive TC] and ORR follow-up [8.7 months] at the March 2021 DCO). However, the EAG considers that as the LIBRETTO-321 trial reports data for patients treated with selpercatinib, it provides

relevant supportive evidence (see Appendix 1, Section 8.1 for brief details of, and results from, the LIBRETTO-321 trial).

Of the 22 studies included in the SLR that provided evidence for comparators, the company included data from the following three trials in indirect comparisons (see Table 6 for references):

- EXAM trial[36] (cabozantinib versus placebo)
- SELECT trial[41] (lenvatinib versus placebo)
- DECISION trial[38] (sorafenib versus placebo).

In addition to the trials identified via the SLR, the company presented "late-breaking data" (CS, p34) from the LIBRETTO-531 trial, an RCT that compared selpercatinib versus physician's choice; patients in the control arm could receive cabozantinib (a relevant comparator for this appraisal) or vandetanib (not a relevant comparator for this appraisal). The interim LIBRETTO-531 trial results were published on 21 October 2023 (9 days before the EAG received the CS). This may explain why the trial was not included in the company SLR.

Descriptions and critiques of the LIBRETTO-001 and LIBRETTO-531 trials are presented in Section 3.2 to Section 3.9. A description and critique of the indirect trial evidence is presented in Section 3.10 to Section 3.13.

The references for all the relevant trials included in the CS and EAG report are presented in Table 6.

Table 6 Trials from which information is presented in the CS and EAG report

Trial/ treatment(s)	Reference	Note
LIBRETTO-001 selpercatinib	Wirth 2019[42]	Primary reference cited for inclusion into the company's SLR (sometimes mis-labelled as Wirth 2018); published as a conference abstract only
	LIBRETTO-001 CSR (13 January 2023 DCO)[31]	Main source for all data provided by the company in the CS. Most of the data presented in the CS and all sections of this EAG report is also reported in the CSR
	LIBRETTO-001 TSAP version 1[43]	Supplementary material to the published paper for the LIBRETTO-001 trial NSCLC population. Used to inform Section 3.7.1 and Appendix 2 (Section 8.2) of this EAG report
	LIBRETTO-001 TSAP version 3[35]	Provided by the company with the CS. Used to inform Section 3.7.1 and Appendix 2 (Section 8.2) of this EAG report
	LIBRETTO-001 protocol version 8[43]	Supplementary material to the published paper for the LIBRETTO-001 trial NSCLC population. Used to inform Section 3.7.1 and Appendix 2 (Section 8.2) of this EAG report
LIBRETTO-321 selpercatinib	Zheng 2022[44]	Primary reference included in feasibility assessment for ITCs in CS, Appendix D.1.3, Table 16 to Table 18. Excluded by the company in the CS but information presented by the EAG in this report extracted from this paper (Appendix 1, Section 8.1 of this EAG report)
LIBRETTO-531 selpercatinib vs physician's choice (cabozantinib or vandetanib)	Hadoux 2023[32]	Primary reference for the only RCT of selpercatinib. Most of the data presented in the CS and all relevant sections of this EAG report is also reported in this paper (i.e., all data which are not are marked as confidential)
	LIBRETTO-531 TSAP version 3[32]	Provided as an appendix to Hadoux 2023. Used to inform Section 3.7.1 and Appendix 2 (Section 8.2) of this EAG report
	LIBRETTO-531 protocol (amendment)[32]	Provided as an appendix to Hadoux 2023. Used to inform Section 3.7.1 and Appendix 2 (Section 8.2) of this EAG report
EXAM cabozanatinib vs placebo	Elisei 2013[36]	Primary reference cited for inclusion into the company's SLR. Used to inform trial and baseline characteristics (Section 3.10.4 and Section 3.10.5 of this EAG report)
	EXAM trial protocol[36]	Provided as an appendix to Elisei 2013. Used to inform Section 3.12.1 of this EAG report
	Sherman 2016[45]	Provides PFS data used in the indirect comparisons (Section 3.10.4 and Section 3.10.5 of this EAG report)
	Schlumberger 2017[46]	Provides OS data used in the indirect comparisons (Section 3.10.4 and Section 3.10.5 of this EAG report). Baseline characteristics for *RET*-mutant subgroup taken from the supplementary appendix (supp table 2)
SELECT lenvatinib vs placebo	Schlumberger 2015[37]	Primary reference cited for inclusion into the company's SLR. Used to inform trial and baseline characteristics (Section 3.11.1 and Section 3.11.2 of this EAG report) and to provide PFS data used in the indirect comparisons (Section 3.11.4 and Section 3.11.5)
	Eisai CS for MTA[41]	Provides OS data used in the indirect comparisons (Section 3.11.1 and Section 3.11.2 of this EAG report). Used to inform quality assessment (Section 3.11.3 of this EAG report)
DECISION sorafenib vs placebo	Brose 2014[38]	Primary reference cited for inclusion into the company's SLR. Used to inform trial and baseline characteristics and quality assessment (Section 3.11.1 to Section 3.11.3 of this EAG report). Provides PFS and OS data used in the indirect comparisons (Section 3.11.4 and 3.11.5 of this EAG report)
	Schlumberger 2013 [47]	Provides HRQoL data. Used to inform Section 3.12.2 of this EAG report
	Bayer CS for MTA[41]	Provides HRQoL data. Used to inform Section 3.12.2 of this EAG report

AE=adverse event; CS=company submission; DCO=data cut-off; EAG=External Assessment Group; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection; SLR=systematic literature review

3.3 *Selpercatinib trials*

3.3.1 LIBRETTO-001 trial

The LIBRETTO-001 trial is an ongoing, multi-centre, international, open-label, phase I/II single-arm basket trial that enrolled patients with solid tumours treated with selpercatinib. The trial started in May 2017 and is being conducted in 16 countries (UK, Denmark, France, Germany, Italy, Spain, Switzerland, United States, Canada, Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan and Israel).

The LIBRETTO-001 trial started as a phase I dose escalation study that enrolled patients with and without *RET* alterations. Based on phase I trial results, the Safety Review Committee (SRC) recommended that the starting dose for phase II of the LIBRETTO-001 study should be 160mg BID.

The LIBRETTO-001 trial is currently in phase II; this is a dose expansion phase and only patients with *RET* alterations receive selpercatinib (160mg BID) every 28 days until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation. Patients may continue to receive treatment with selpercatinib beyond disease progression if a clinician considers that the patient is continuing to benefit.

The primary outcome is ORR by a blinded Independent Review Committee (IRC); other key outcomes include IRC-assessed PFS, OS, HRQoL and adverse events (AEs). Most of the data presented in the CS are from the 13 January 2023 data cut-off (DCO). Additional data, from earlier DCOs (16 December 2019 and 15 June 2021) are provided in CS, Appendix N.3.

[redacted]

LIBRETTO-001 trial inclusion criteria and patient characteristics

Key LIBRETTO-001 trial inclusion criteria are patients aged ≥18 years (aged ≥12 years where permitted by local regulatory authorities) with locally advanced or metastatic solid tumours (i.e., patients with *RET* fusion-positive non-small cell lung cancer [NSCLC], pancreatic cancer or colorectal cancer, and patients with other agnostic tumours with *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.

Full eligibility criteria are presented in the CS (Table 6). To date, 837 patients have been enrolled in the LIBRETTO-001 trial and received at least one dose of selpercatinib. It is unknown how many patients met each inclusion criterion (Clarification Question A1 and A2).

Details of the seven LIBRETTO-001 trial population analysis sets described in the CS are provided in Table 7. All analyses included patients from phase I and phase II of the trial (LIBRETTO-001 trial CSR,[31] p53).

Table 7 LIBRETTO-001 trial: population analysis sets

Population	Description
RET-mutant MTC cabozantinib/ vandetanib-naïve (n=143)	Efficacy eligible patients[a] that have had no prior systemic therapy or have been treated with a prior systemic therapy besides cabozantinib and vandetanib at the 13 January 2023 DCO
RET-mutant MTC any-line (n=295)[b]	All efficacy eligible patients[a] (including patients previously treated with a systematic therapy) with *RET*-mutant MTC at the 13 January 2023 DCO
RET-mutant MTC efficacy analysis set (n=[redacted])	All efficacy eligible patients[a] (including patients previously treated with a systematic therapy) with *RET*-mutant MTC and including patients with non-measurable disease (n=[redacted]) at the 13 January 2023 DCO
RET fusion-positive TC systemic therapy-naïve (n=24)	Efficacy eligible patients[a] who have received no prior systemic therapy other than radioactive iodine at the 13 January 2023 DCO
RET fusion-positive TC any-line (n=65)	All efficacy eligible patients[a] (including patients previously treated with a systematic therapy) with *RET* fusion-positive TC at the 13 January 2023 DCO
RET-mutant MTC MTC safety (n=324)	All patients with *RET*-mutant MTC (including patients previously treated with a systematic therapy) who received ≥1 dose of selpercatinib at the 13 January 2023 DCO
RET fusion-positive TC safety (n=66)	All patients with *RET* fusion-positive TC (including patients previously treated with a systematic therapy) who received ≥1 dose of selpercatinib in LIBRETTO-001 at the 13 January 2023 DCO
OSAS (n=837)	All patients who received ≥1 dose of selpercatinib (including patients previously treated with a systematic therapy) regardless of diagnosis (i.e., includes patients with *RET*-mutant MTC [n=324], RET fusion-positive TC [n=66], NSCLC [n=362], other solid tumours [n=55) and other cancers [n=30] at the 13 January 2023 DCO

[a] Patients who had received ≥1 dose of selpercatinib and had achieved ≥6 months of patient follow-up time from this first dose of selpercatinib (or disease progression or death, whichever occurred first) as of 13 January 2023 were considered eligible for efficacy analyses
[b] Excludes [redacted] patients with non-measurable disease
CS=company submission; DCO=data cut-off; MTC=medullary thyroid cancer; NSCLC=non-small cell lung cancer; OSAS=overall safety analysis set population; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, adapted from Table 5 and Figure 7

3.3.2 LIBRETTO-531 trial

The LIBRETTO-531 trial is an ongoing, multi-centre, international, open-label, phase III trial that started in February 2020. Patients aged ≥18 years (aged ≥12 years where permitted by local regulatory authorities) were randomised 2:1 to receive first-line treatment with either selpercatinib (160mg BID for adults or 92mg/m^2 BID for patients aged 12 to 18 years) or

physician's choice (cabozantinib 140mg once daily [QD] or vandetanib 300mg QD). The LIBRETTO-531 trial only included patients who were cabozantinib/vandetanib-naïve.

Since November 2021, patients assigned to the physician's choice arm since have only been treated with cabozantinib because of the "fluctuating availability of vandetanib".[32] The LIBRETTO-531 trial is being conducted in 21 countries (United Kingdom, Belgium, Czechia, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Russian Federation, United States, Canada, Brazil, Australia, China, Japan, South Korea, India, Taiwan and Israel). The key inclusion criteria are:

- pathologically confirmed, unresectable, locally advanced or metastatic MTC with a *RET* alteration (somatic or germline) and
- no history of treatment with kinase inhibitors.

The full LIBRETTO-531 trial eligibility criteria are presented in the CS (Appendix M, Table 62). Patients receive selpercatinib or cabozantinib/vandetanib in 28-day cycles until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation. Patients are permitted to receive treatment with selpercatinib beyond disease progression if the clinician considers that the patient is continuing to benefit. Patients randomised to physician's choice may be eligible to crossover to selpercatinib treatment on disease progression confirmed by IRC. Selpercatinib, cabozantinib and vandetanib dose adjustments are permitted.

In total, 291 patients were randomised to either selpercatinib (n=193) or to physician's choice (n=98). A protocol-specified interim efficacy analysis was scheduled to be triggered after at least 56 (progression or death) events had occurred and was performed after 59 events had occurred (22 May 2023 DCO). The primary outcome is IRC-assessed PFS; other key outcomes include OS, IRC-assessed and investigator-assessed ORR, IRC-assessed and investigator-assessed duration of response (DoR), HRQoL and AEs.

The number of patients who received selpercatinib was n=193 in the efficacy and safety populations. Approximately three-quarters of LIBRETTO-531 trial physician's choice arm patients received cabozantinib. The number of patients randomised to cabozantinib and vandetanib was n=71 and n=27, respectively (intention-to-treat [ITT] population). However, due to supply issues, the actual number of patients who received cabozantinib and vandetanib was n=71 and n=27, respectively (subgroup efficacy analyses populations).

The EAG considers that the LIBRETTO-531 trial clinical effectiveness evidence is likely to be the most relevant for patients with *RET*-mutant MTC for this appraisal; all LIBRETTO-531 trial patients were cabozantinib/vandetanib-naïve and the trial provides direct evidence for the

most relevant comparator (cabozantinib). However, the EAG acknowledges that the LIBRETTO-531 trial[32] data (start date: February 2020, latest DCO available: 22 May 2023) has substantially shorter follow-up than the LIBRETTO-001 trial[31] data (trial start date: May 2017, latest DCO available: 13 January 2023).

3.4 *LIBRETTO-001 and LIBRETTO-531 trials RET-mutant MTC: patient characteristics*

LIBRETTO-001 and LIBRETTO-531 trial baseline characteristics for patients with *RET*-mutant MTC are provided in Table 8. In the LIBRETTO-001 trial, most patients (systemic therapy-naïve: n=[redacted], [redacted]; any-line: n=[redacted], [redacted]) were from North America (CSR,[31] Table 1.1); there were [redacted] UK patients (Clarification Question A3). Approximately half of the LIBRETTO-531 trial patients were treated in Europe (n=165, 56.7%), with a similar proportion of patients treated in Europe in each treatment arm; the proportion of patients treated in the UK was not reported. Despite these differences, clinical advice to the EAG is that the characteristics of LIBRETTO-001 and LIBRETTO-531 trial patients broadly reflect NHS patients, with the following exceptions:

- a slightly higher proportion of patients were men in both trials than in NHS clinical practice; clinical advice to the EAG is that the incidence of thyroid cancer is higher in women than men but that men with thyroid cancer have a poorer prognosis than women with thyroid cancer
- a higher proportion of patients were Asian in the LIBRETTO-531 trial than expected in NHS clinical practice.

Clinical advice to the EAG is that the differences in patient characteristics would not influence efficacy or safety results.

Table 8 LIBRETTO-001 and LIBRETTO-531 trials: *RET*-mutant MTC, patient baseline characteristics

Characteristic	*RET*-mutant MTC			
	LIBRETTO-001		LIBRETTO-531	
	Selpercatinib: cabozantinib/ vandetanib-naïve (n=143)	Selpercatinib: any-line (n=295)	Selpercatinib: kinase inhibitor-naïve (n=193)	Physician's choice:[a] kinase inhibitor-naïve (n=98)
Age, median (range) years	57 (15 to 87)	58 (15 to 90)	56 (12 to 79)	54 (18 to 84)
Age <18 years	[redacted]	[redacted]	1 (0.5)	0
Age 18 to <65 years	[redacted]	[redacted]	143 (74.1)	72 (73.5)
Age ≥65 years	[redacted]	[redacted]	49 (25.4)	26 (26.5)
Male, n (%)	83 (58.0)	180 (61.0)	115 (59.6)	68 (69.4)
White, n (%)	124 (86.7)	[redacted]	116 (60.1)	52 (53.1)
Asian, n (%)	8 (5.6)	[redacted]	43 (22.3)	24 (24.5)
ECOG PS ≥1, n (%)	74 (51.7)	184 (62.4)	70 (36.3)	42 (42.9)
Stage IV disease	134 (93.7)	[redacted]	NR	NR
RET mutation M918T	86 (60.1)	[redacted][b]	121 (62.7)	61 (62.2)
Median (range) time from diagnosis of metastatic disease, months[c]	[redacted]	[redacted]	42.7 (15.2 to 98.9)	61.6 (20.2 to 141.0)
Patients with measurable disease, n (%)	[redacted]	[redacted]	NR	NR
Received prior kinase inhibitor, n (%)	9 (6.3)	[redacted]	0	0
Received any prior systemic therapy, n (%)	[redacted]	[redacted]	0	0

[a] Cabozantinib (n=73) or vandetanib (n=25)
[b] Reported as a proportion of the *RET*-mutant MTC efficacy analysis set (n=[redacted]) patients as *RET* mutation status data were unavailable for the any-line *RET*-mutant MTC population (n=295)
[c] Median (range) of [redacted] cabozantinib/vandetanib-naïve patients and [redacted] any-line patients in LIBRETTO-001 trial
CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; MTC=medullary thyroid cancer; NR=not reported; *RET*=rearranged during transfection
Source: CS, Table 7 to Table 8; Zheng 2022[44] and ClinicalTrials.gov;[48] Hadoux 2023[32]

There were some differences in patient characteristics between the LIBRETTO-001 and LIBRETTO-531 trials:

- a higher proportion of patients in the LIBRETTO-001 trial had ECOG PS ≥1 than in the LIBRETTO-531 trial
- a smaller proportion of patients in the LIBRETTO-001 trial were Asian than in the LIBRETTO-531 trial
- the LIBRETTO-531 trial *only* included patients with RET-mutant MTC who had not received previous treatment for advanced thyroid cancer (i.e., the population defined in the final scope issued by NICE).

In the LIBRETTO-001 trial, [redacted] ([redacted]/143) of patients in the cabozantinib/vandetanib-naïve population had received prior systemic therapy including a small proportion (9/143, 6.3%) of patients who had received kinase inhibitors other than cabozantinib or vandetanib; clinical advice to the EAG is that patients with MTC only receive systemic therapy with MKIs for advanced disease.

There were some expected differences in patient characteristics by line of treatment in the LIBRETTO-001 trial:

- a higher proportion of any-line patients had ECOG PS≥1 (62.4%), compared with cabozantinib/vandetanib-naïve patients (51.7%)
- the median (range) number of previous lines of systemic therapy was 0 (0 to 2) in the cabozantinib/vandetanib-naïve population and [redacted] ([redacted] to [redacted]) in the any-line MTC population.

The following LIBRETTO-531 differences between treatment arms were identified:

- a higher proportion of patients were male in the physician's choice arm (69.4%) than in the selpercatinib arm (59.6%)
- time from diagnosis of metastatic disease to trial entry was longer in the physician's choice arm (61.6 months) than in the selpercatinib arm (42.7 months).

It is unclear if these differences would bias the results in favour of one treatment arm over the other.

3.5 *LIBRETTO-001 RET fusion-positive TC: patient characteristics*

LIBRETTO-001 trial baseline characteristics for patients with *RET* fusion-positive TC treated with selpercatinib are presented in Table 9. Approximately two-thirds of patients (systemic therapy-naïve: n=[redacted], [redacted]; any-line: n=[redacted], [redacted]) were from North America (CSR,[31] Table 1.1); there were [redacted] UK patients (Clarification Question A3). Nonetheless, clinical advice to the EAG is that the characteristics of LIBRETTO-001 trial patients broadly reflect the characteristics of NHS patients, except that:

- a slightly higher proportion of patients were men in the trial than in NHS clinical practice; the incidence of thyroid cancer is higher in women than men

- a higher proportion of patients were Asian and a higher proportion of patients had central nervous system (CNS) metastases in the any-line *RET* fusion-positive TC population ([redacted]) than in NHS clinical practice.

Clinical advice to the EAG is that the differences in patient characteristics would not influence efficacy or safety results.

Table 9 LIBRETTO-001 trial: *RET* fusion-positive TC, patient baseline characteristics

Characteristic	*RET* fusion-positive TC	
	Selpercatinib: systemic therapy-naïve (n=24)	Selpercatinib: any-line (n=65)
Age, median (range) years	60.5 (20 to 84)	59 (20 to 88)
Age <65 years	[redacted][a]	[redacted][a]
Age ≥65 years	[redacted]	[redacted]
Male, n (%)	[redacted]	32 (49.2)
White, n (%)	18 (75.0)	[redacted]
Asian, n (%)	1 (4.2)	[redacted]
ECOG PS ≥1, n (%)	10 (41.7)	40 (61.5)
Stage IV disease	24 (100.0)	[redacted]
Papillary	[redacted]	[redacted]
Poorly differentiated	[redacted]	[redacted]
Hürthle cell	[redacted]	[redacted]
Anaplastic	[redacted]	[redacted]
Missing or non-diagnosed	[redacted]	[redacted]
Median (range) time from diagnosis of metastatic disease, months	[redacted]	[redacted]
Received prior kinase inhibitor, n (%)	0	[redacted]
Received any prior systemic therapy, n (%)	[redacted][b]	[redacted]

[a] No patients were aged <18 years
[b] In the *RET* fusion-positive systemic therapy-naïve population, the only previous systemic therapy was radioactive iodine therapy
CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; MTC=medullary thyroid cancer; NR=not reported; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 9 to Table 11

There were some differences in patient characteristics by line of treatment:

- a higher proportion of patients in the any-line population had ECOG PS ≥1 than in the systemic therapy-naïve population
- median time from diagnosis of metastatic disease was a [redacted] in the any-line population than in the systemic therapy-naïve population
- median (range) number of previous lines of systemic therapy was 1 (0 to 5) in the systemic therapy-naïve *RET* fusion-positive TC population and [redacted] ([redacted] to [redacted]) in the any-line *RET* fusion-positive TC population.

In the *RET* fusion-positive systemic therapy-naïve population, the only previous systemic therapy was radioactive iodine therapy. Clinical advice to the EAG is that these patients can therefore be considered to be previously untreated for advanced TC.

3.6 *LIBRETTO-001 and LIBRETTO-531 trial: quality assessment*

The company conducted a quality assessment of the LIBRETTO-001 trial using the Critical Appraisal Skills Programme (CASP)[39] checklist for cohort studies. The responses to each quality item on the CASP[39] checklist are either, 'yes', 'no' or 'cannot tell'.

The company's assessment of the LIBRETTO-001 trial with EAG comment is presented in Table 10. The EAG's main concerns with the quality of the trial surround the trial design and inclusion criteria. Single-arm trials tend to be at higher risk of selection bias and confounding than RCTs. Furthermore, the EAG is uncertain whether the patients who were enrolled into the trial were comparable to patients who would receive current standard therapy in NHS clinical practice (cabozantinib, lenvatinib or sorafenib). The uncertainty is because the stated eligibility criteria (CS, Table 3, p37) included patients 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.

It was unclear what was meant by standard therapy in the context of the trial eligibility criteria given the trial was multinational, meaning standard therapy may have differed across countries and so standard therapy may have included or excluded cabozantinib, lenvatinib or sorafenib.

To try and better understand the type of patients being enrolled, the EAG requested further information regarding the number of patients who were included for each of the above reasons during clarification (Clarification Question A1 and A2). However, the company was unable to provide the data (other than patients who progressed on prior standard therapy) as the exact criteria fulfilled to permit enrolment was not recorded for individual patients.

Table 10 LIBRETTO-001 trial: quality assessment

Quality assessment item	Company assessment	EAG assessment and comment
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 selpercatinib in patients with advanced solid tumours, including *RET* fusion-positive solid tumours, MTC, and other tumours with *RET* activation. Clear, pre-specified inclusion and exclusion criteria for patients and clearly defined endpoints were used. For Part I of the study, the primary endpoint was the MTD of selpercatinib. For Part II of the study, this was ORR as assessed by IRC. Secondary endpoints are also clearly listed.	Yes
2. Was the cohort recruited in an acceptable way?	Clear and pre-specified inclusion and exclusion criteria are presented in the CSR. However, LIBRETTO-001 is an open-label, single-arm study which could create selection bias.	Cannot tell The LIBRETTO-001 is an open-label, single-arm and therefore has high risk of selection bias. In the inclusion criteria, it was specified that standard therapy must be unsuitable or unacceptable for patients or patients must have declined standard therapy, however, standard therapy was not defined
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.	Yes
4. Was the outcome accurately measured to minimise bias?	Yes Validated objective measurements were used. Response based endpoints, including ORR and PFS, were measured based on RECIST v1.1 criteria and assessed by an IRC. Adverse events were not assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as the trial is an open-label, single-arm study.	Yes
5a. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	n/a LIBRETTO-001 is a single-arm trial	Yes Confounding factors are important to identify in any study, particularly single arm trials. Clinical advice to the EAG is that important confounding factors (age, sex, ECOG PS, smoking status, *RET* M918T mutation status and prior MKI treatment) were considered in the company's pre-planned subgroup analyses

Quality assessment item	Company assessment	EAG assessment and comment
5b. Have they taken account of the confounding factors in the design and/or analysis?	n/a LIBRETTO-001 is a single-arm trial	Yes Clinical advice to the EAG is that important confounding factors (age, sex, ECOG PS, smoking status, *RET* M918T mutation status and prior MKI treatment) were considered in the company's pre-planned subgroup analyses
6a. Was the follow up of subjects complete enough?	Yes Patients underwent regular assessments for response in line with the pre-specified assessment schedule	Yes At the 13 January 2023 DCO, [redacted] of patients were lost to follow-up
6b. Was the follow up of subjects long enough?	Yes Based on the 13th January 2023 data cut, median duration of follow-up for OS was [redacted] and [redacted] for the MTC and the TC patient populations of relevance to this submission, respectively. This duration of follow-up is broadly consistent with duration of follow-up observed in trials for comparator treatments in similar indications. Further follow-up would be informative to more accurately characterise long-term survival	Yes
7. What are the results of this study?	Selpercatinib was well-tolerated and had marked antitumour activity in *RET*-altered TC and MTC and NSCLC patients, including those with resistance to prior MKIs and brain metastases from the initial results presented	Yes However, the results cannot be directly compared against a comparator of interest (cabozantinib, lenvatinib, sorafenib, BSC)
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	Cannot tell The results were precise for some key outcomes (ORR, DoR, PFS and OS rates) where the 95% CI could be estimated but unprecise for median PFS and median OS [redacted]
9. Do you believe the results?	Yes The results of the LIBRETTO-001 trial remain consistent across all three reported DCOs (December 2019, June 2021, January 2023) in the TC and MTC populations. IRC assessment was used to minimise bias, and increased sample sizes are available for the January 2023 DCO	Yes However, the LIBRETTO-001 trial is an ongoing single-arm trial with few survival events to date

Quality assessment item	Company assessment	EAG assessment and comment
10. Can the results be applied to the local population?	Yes These results can be applied to other TC, MTC and NSCLC patients with *RET*-altered tumours.	Cannot tell It is not clear whether LIBRETTO-001 trial patients with untreated advanced MTC and TC are representative of NHS patients with untreated advanced MTC and TC. In the LIBRETTO-001 inclusion criteria, it was specified that standard therapy must be unsuitable or unacceptable for patients, or patients must have declined standard therapy; NHS patients would be eligible for standard therapy (cabozantinib, lenvatinib, sorafenib). Patients with NSCLC are not relevant to this appraisal
11. Do the results of this study fit with other available evidence?	No targeted therapy is approved for patients with *RET*-altered tumours in the first-line. However, the results of this study are aligned with preliminary data from LIBRETTO-531.	Yes The LIBRETTO-001 trial results are consistent with LIBRETTO-531 trial results for patients with *RET*-mutant MTC; however, the LIBRETTO-001 trial ORR results are more favourable for selpercatinib than the LIBRETTO-531 trial selpercatinib ORR results. The LIBRETTO-001 and LIBRETTO-531 trials have unprecise results for median PFS and median OS [redacted]
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as an effective and well-tolerated therapy for TC, MTC and NSCLC patients with *RET*-altered tumours.	Cannot tell The LIBRETTO-001 trial results appear to be favourable for selpercatinib but the LIBRETTO-001 trial does not provide direct comparative data versus relevant comparators (cabozantinib, lenvatinib, sorafenib, BSC) necessary to inform decision making

BSC=best supportive care; CI=confidence interval; CS=company submission; CSR=Clinical Study Report; CTCAE=common terminology criteria for adverse events; DCO=data cut-off; DoR=duration of response; EAG=External Assessment Group; IRC=independent review committee; MKI=multikinase inhibitor; MTC=medullary thyroid cancer; MTD=maximum-tolerated dose; n/a=not applicable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; *RET*=rearrangements and/or mutations during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 19

The company conducted quality assessment of the LIBRETTO-531 (Clarification Question A16) using the quality assessment checklist for clinical trials[49] devised by the Centre for Reviews and Dissemination (CRD) at the University of York. The company's assessments and ERG comments are presented in Table 11. The EAG considers that the LIBRETTO-531 trial is of good methodological quality and has low risk of bias.

Table 11 LIBRETTO-531 trial: quality assessment

Parameter	Company assessment	EAG assessment and comment
Was randomisation carried out appropriately?	Yes Eligible patients were allocated to two arms in a 2:1 ratio to receive selpercatinib or control (cabozantinib or vandetanib), respectively	Unclear The method of randomisation was not reported, e.g., random numbers generated by computer
Was the concealment of treatment allocation adequate?	No This was an open-label study between selpercatinib and physician's choice (cabozantinib/vandetanib). However, the sponsor was blinded to the aggregate data (i.e., did not review or analyse data).	Unclear Methods to conceal treatment allocation were not reported
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes The treatment arms are well balanced except for the gender difference. Regarding the difference in median time from diagnosis to baseline, the confidence intervals are very wide. It is unclear as to whether this is a meaningful difference. The relative indolent nature of MTC with large variations in records of time of diagnosis could be the reason for the above. Eligibility criteria for LIBRETTO-531 included progressive disease within 14 months of baseline, confirmed by BICR	Yes Most baseline characteristics were balanced. However, a higher proportion of patients were male in the physician's choice arm (69.4%) than in the selpercatinib arm (59.6%) and time from diagnosis of metastatic disease to trial entry was longer in the physician's choice arm (61.6 months) than in the selpercatinib arm (42.7 months)
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No This was an open-label study; hence, allocations were not masked from the patient or the investigator. However, the outcomes were assessed by BICR	No
Were there any unexpected imbalances in dropouts between groups?	Yes Proportions of dropouts (Protocol deviations, withdrawal by patients, patients who did not receive treatment): The patient dropouts were higher in the control arm (9.1% [9/98]) when compared to the selpercatinib arm (2.5% [5/193]). Proportions of total treatment discontinuations: All-cause discontinuations were higher in the control arm (58% [57/98]) when compared to the selpercatinib arm (9.3% [18/193])	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No The authors reported the efficacy and safety endpoints that were described in the methods section	No DoR results only provided in the CS, not the published paper[32]

Parameter	Company assessment	EAG assessment and comment
Did the analysis include an intention-to-treat analysis? If so, was this appropriate, and were appropriate methods used to account for missing data?	Yes ITT analysis was performed. All members of both the arms were included and analysed as part of the group they were assigned to. None of the patients took wrong medication, all were treated with the assigned therapy in both arms. The data for dropouts and reasons were also mentioned in the CONSORT diagram	Yes

BICR=blinded independent committee review; CONSORT=Consolidated Standards of Reporting Trials; CS=company submission; DoR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; ITT=intention-to-treat; MTC=medullary thyroid cancer; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor
Source: Clarification Question A16, Table 15

3.7 *Direct clinical effectiveness results from the selpercatinib trials*

LIBRETTO-001 and LIBRETTO-531 trial results are summarised in Section 3.7.2 to Section 3.7.4. The LIBRETTO-001 trial primary outcome was IRC-assessed ORR and the LIBRETTO-531 trial primary outcome was IRC-assessed PFS.

3.7.1 LIBRETTO-001 trial and the LIBRETTO-531 trial: statistical analysis approach

Information relevant to the statistical approach taken by the company to analyse LIBRETTO-001 trial data has been extracted from the CSR (13th January 2023),[31] the trial statistical analysis plan (TSAP) version 1[43] and version 3,[35] the trial protocol version 8,[43] and the CS. Information relevant to the statistical approach taken by the company to analyse LIBRETTO-531 trial data has been extracted from the trial statistical analysis plan version 3 (TSAP),[32] the trial protocol (amendment h),[32] and the CS. The LIBRETTO-531 trial CSR was unavailable at the time of the company's response to NICE's clarification letter (Clarification Question C1). A summary of the EAG checks of the pre-planned statistical approaches used by the company to analyse data from the LIBRETTO-001 and LIBRETTO-531 trials is provided in Appendix 2, Section 8.2 of this EAG report. Overall, the EAG considers that the statistical approaches taken by the company were appropriate.

The company employed a multiple testing strategy when analysing LIBRETTO-531 trial[32] data. At the time of the interim analysis, statistical significance for PFS was determined if the two-sided p-value was less than 0.003. Treatment failure-free survival (TFFS) was to be tested against a two-sided significance level of 0.05 only if PFS results were significant. Other outcomes were not accounted for in the multiple testing strategy, and p-values should not be used to infer statistical significance.

3.7.2 LIBRETTO-001 trial efficacy results: *RET*-mutant MTC

Duration of follow-up

The company presented (CS, Section B.2.6.1) LIBRETTO-001 trial results from the most recent DCO (13 January 2023).[31] Trial key secondary outcome results (PFS and OS only) from earlier DCOs are provided in CS, Appendix N.3. The median duration of follow-up varied by outcome (Table 12).

Table 12 LIBRETTO-001 trial: *RET*-mutant MTC populations, median duration of follow-up for key efficacy outcomes

Median duration of follow-up	Selpercatinib *RET*-mutant cabozantinib/ vandetanib-naïve (n=143)	Selpercatinib *RET*-mutant any-line (n=295)
DoR (relating to primary outcome of ORR), months	39.4	[redacted]
PFS, months	42.4	[redacted]
OS, months	[redacted]	[redacted]

CS=company submission; DoR=duration of response; MTC=medullary thyroid cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival *RET*=rearranged during transfection
Source: CS, Table 21 to Table 23

Key efficacy results

Key efficacy outcome results from the latest DCO (13 January 2023)[31] are summarised in Table 13. Patients were permitted to continue to receive treatment with selpercatinib beyond disease progression if a clinician considered that the patient was continuing to benefit. As reported in the CS (Table 15) and in the clarification response (Clarification Question A3), some patients in the cabozantinib/vandetanib-naïve and any-line populations received selpercatinib beyond progression: [redacted]/143 ([redacted]) and [redacted]/295 ([redacted]), respectively.

Table 13 LIBRETTO-001 trial: cabozantinib/vandetanib-naïve and any-line *RET*-mutant MTC populations, key efficacy results

Outcome	*RET*-mutant MTC cabozantinib/vandetanib-naïve (n=143)		*RET*-mutant MTC any-line (n=295)	
	IRC-assessed (n=143)	Investigator-assessed (n=143)	IRC-assessed (n=295)	Investigator-assessed (n=295)
ORR, n (% [95% CI])	118 (82.5 [75.3 to 88.4])	[redacted]	[redacted]	NR
CR, n (%)	34 (23.8)	[redacted]	[redacted]	NR
PR, n (%)	84 (58.7)	[redacted]	[redacted]	NR
Median DoR (range), months	NE (51.3 to NE)	[redacted]	[redacted]	NR
DoR rate ≥12 months (95% CI)	91.4 (84.6 to 95.3)	[redacted]	[redacted]	NR
DoR rate ≥24 months (95% CI)	84.1 (75.9 to 89.7)	[redacted]	[redacted]	NR
DoR rate ≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
DoR rate ≥48 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
DoR rate ≥60 months (95% CI)	[redacted]	Not assessed	[redacted]	NR
Patients who progressed or died, n (%)	[redacted]	[redacted]	[redacted]	NR
Median PFS, months (range)	NE (53.1 to NE)	[redacted]	[redacted]	NR
PFS rate ≥12 months (95% CI)	91.1 (84.8 to 94.8)	[redacted]	[redacted]	NR
PFS rate ≥24 months (95% CI)	82.5 (74.8 to 88.0)	[redacted]	[redacted]	NR
PFS rate ≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
PFS rate ≥48 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
PFS rate ≥60 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
Patients who died, n (%)	[redacted]		[redacted]	
Median OS, months (range)	[redacted]		[redacted]	
OS rate ≥12 months (95% CI)	[redacted]		[redacted]	
OS rate ≥24 months (95% CI)	[redacted]		[redacted]	
OS rate ≥36 months (95% CI)	[redacted]		[redacted]	
OS rate ≥48 months (95% CI)	[redacted]		[redacted]	

CI=confidence interval; CR=complete response; CS=company submission; DoR=duration of response; IRC=Independent Review Committee; MTC=medullary thyroid cancer; NE=not estimable; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; *RET*=rearranged during transfection
Source: CS, Table 20 to Table 23, CS Appendix N1.1, p143, Table 68 to Table 70, Clarification Question A10 and Clarification Question A11

A high proportion of LIBRETTO-001 trial patients obtained an IRC-assessed complete response (CR) or partial response (PR) to treatment. The results suggest a greater treatment effect in the cabozantinib/vandetanib-naïve population than in the any-line population.

The company highlighted (CS, p71) that Waterfall plots showing the best change in tumour size for patients demonstrated that tumours were reduced by >25% for most patients in the cabozantinib/vandetanib-naïve population (CS, Figure 10) and in the any-line population (CS, Figure 11). DoR was [redacted] in either population because too few patients who achieved ORR (CR or PR) subsequently progressed and/or died; most patients who achieved an ORR were still responding to treatment at the time of the 13 January 2023 DCO (as shown by the DoR rates in Table 13). Similarly, median PFS and median OS [redacted] in either population.

Investigator-assessed results

The company has presented results, by investigator assessment, for tumour response and disease progression for the cabozantinib/vandetanib-naïve population also (CS, Appendix N1.1). These investigator-assessed results were largely similar to IRC-assessed results. [redacted].

Results from subgroup analyses

The company presented (CS, Section 2.7.1) subgroup analysis results for patients with cabozantinib/vandetanib-naïve MTC by type of RET mutation, type of molecular assay used, and the number and types of prior therapy for IRC-assessed ORR and DoR. The subgroup analysis results were broadly consistent with the overall cabozantinib/vandetanib-naïve population results. For most subgroups, DoR was [redacted].

3.7.3 LIBRETTO-531 trial efficacy results: *RET*-mutant MTC

Duration of follow-up

LIBRETTO-531 trial interim efficacy analyses (May 2023 DCO) are reported in the CS (Section B.2.6.3 and Appendix M) median PFS follow-up was [redacted] months. Duration of follow-up varied by outcome and treatment arm (Table 14). LIBRETTO-531 trial[32] data have substantially shorter follow-up than LIBRETTO-001 trial[31] data (LIBRETTO-001 trial cabozantinib/vandetanib-naïve *RET*-mutant MTC population median DoR follow-up: 39 months; PFS follow-up: 42 months; median OS follow-up: [redacted] months).

Table 14 LIBRETTO-531 trial: *RET*-mutant MTC population, median duration of follow-up for key efficacy outcomes

Median duration of follow-up	Selpercatinib (n=193)	Physician's choice (n=98)
PFS (primary outcome), months	[redacted]	[redacted]
Treatment failure-survival, months	[redacted]	[redacted]
OS, months	[redacted]	

[a] Data reported for the trial as a whole
MTC=medullary thyroid cancer; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection
Source: Hadoux 2023[32]

Key efficacy results

Key efficacy results are presented in Table 15. Patients were permitted to continue to receive treatment with selpercatinib beyond disease progression if a clinician considered that the patient was continuing to benefit. Data regarding patients who continued treatment with selpercatinib beyond progression were not reported. Patients randomised to physician's choice were eligible to crossover to selpercatinib on disease progression confirmed by IRC. To date, 24 patients (77.4% of 31 who were eligible and 24.5% of all physician's choice arm patients) received selpercatinib; 19/24 (79.2%) are still receiving treatment with selpercatinib. OS results are therefore confounded by treatment crossover.

Table 15 LIBRETTO-531 trial: cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC, key efficacy results

Outcome[a]	Selpercatinib (n=193)	Physician's choice (n=98)
ORR, n (% [95% CI])	[redacted]	[redacted]
CR, n (%)	23 (11.9)	4 (4.1)
PR, n (%)	111 (57.5)	34 (34.7)
Median DoR (95% CI), months	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
Patients who progressed or died, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	NE (NE to NE)	16.8 (12.2 to 25.1)
HR (95% CI); p-value	0.28 (0.16 to 0.48); p<0.001	
PFS rate ≥12 months (95% CI)	86.8 (79.8 to 91.6)	65.7 (51.9 to 76.4)
PFS rate ≥24 months (95% CI)	76.4 (66.5 to 83.8)	37.2 (21.9 to 52.6)
Median TFFS, months (range)	NE (NE to NE)	13.9 (11.3 to 25.1)
HR (95% CI); p-value	0.25 (0.15 to 0.42); p<0.001	
Patients who died, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
OS rate ≥12 months (95% CI)	[redacted]	[redacted]
OS rate ≥24 months (95% CI)	[redacted]	[redacted]

[a] ORR, CR, PR, DoR, TFFS and PFS results are based on Independent Review Committee assessment
CI=confidence interval; CR=complete response; CS=company submission; DoR=duration of response; HR=hazard ratio; MTC=medullary thyroid cancer; NE=not estimable; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; *RET*=rearranged during transfection; TFFS=treatment failure-free survival

Source: CS, Table 32 and Appendix M.2, Figure 9; Hadoux 2023[32]

Patients treated with selpercatinib had better outcomes than patients treated with physician's choice. However, LIBRETTO-531 trial ORRs and PFS and OS rates at ≥12 months and ≥24 months for cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC treated with selpercatinib were lower than in the LIBRETTO-001 trial cabozantinib/vandetanib-naïve *RET*-mutant MTC population. Clinical advice to the EAG is that differences in outcomes may be attributable to differences in patient characteristics between the LIBRETTO-001 and LIBRETTO-531 trials and/or that LIBRETTO-531 trial[32] data has substantially shorter follow-up than LIBRETTO-001 trial[31] data.

Investigator-assessed results

Investigator-assessed LIBRETTO-531 trial results were not reported in the CS. Hadoux 2023[32] reported that investigator-assessed results were "similar" to IRC-assessed results. However, median investigator-assessed PFS (hazard ratio [HR]=0.19) was more favourable to selpercatinib than median IRC-assessed PFS (HR=0.28).

Subgroup analysis results

Across all pre-specified LIBRETTO-531 trial subgroups, PFS was longer for patients treated with selpercatinib than for patients treated with physician's choice (IRC-assessed and investigator-assessed). The subgroup results of most relevance to this appraisal are those for the comparison of selpercatinib versus cabozantinib, presented in Table 16. The EAG agrees with the company (Clarification Question A14) that these initial results show that, compared with cabozantinib, the benefit for patients treated with selpercatinib is clinically meaningful and favours selpercatinib over cabozantinib.

Table 16 LIBRETTO-531 trial: cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC, key subgroup efficacy results (selpercatinib versus cabozantinib)

Outcome	Selpercatinib (n=129)	Cabozantinib (n=71)
ORR, n (% [95% CI]) [a]	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	

[a] Data not provided for complete response, partial response, duration of response or treatment-failure free survival; ORR and PFS results are based on Independent Review Committee assessment
CI=confidence interval; DoR=duration of response; HR=hazard ratio; MTC=medullary thyroid cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection
Source: Clarification Question A14

3.7.4 LIBRETTO-001 trial clinical efficacy results: *RET fusion-positive* TC

Duration of follow-up

The company presented LIBRETTO-001 trial efficacy results from the most recent DCO (13 January 2023); PFS and OS results from earlier DCOs are provided in CS, Appendix N.3. The median duration of follow-up varied by outcome (Table 17).

Table 17 LIBRETTO-001 trial: *RET* fusion-positive TC populations, median duration of follow-up for key efficacy outcomes

Median duration of follow-up	*RET* fusion-positive TC systemic therapy-naïve (n=24)	*RET* fusion-positive TC any-line population (n=65)
DoR (relating to primary outcome of ORR), months	17.8	[redacted]
PFS, months	24.9	[redacted]
OS, months	[redacted]	[redacted]

CS=company submission; DoR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 27 to Table 29

Key efficacy results

Key results from the 13 January 2023 DCO are presented in Table 18. Interpreting systemic therapy-naïve LIBRETTO-001 trial results is challenging due to the small number of patients (n=24). Patients were permitted to continue to receive treatment with selpercatinib beyond disease progression if a clinician considered that the patient was continuing to benefit. As reported in the CS (Table 16), some patients in the systemic therapy-naïve and any-line populations received selpercatinib beyond progression: [redacted]/24 ([redacted]) and [redacted]/65 ([redacted]), respectively.

Table 18 LIBRETTO-001 trial: systemic therapy-naïve and any-line populations with *RET* fusion-positive TC, key efficacy results

Outcome	*RET* fusion-positive TC systemic therapy-naïve (n=24)		*RET* fusion-positive TC any-line (n=65)	
	IRC-assessed (n=24)	Investigator-assessed (n=24)	IRC-assessed (n=65)	Investigator-assessed (n=65)
ORR, n (% [95% CI])	23 (95.8 [78.9 to 99.9])	[redacted]	[redacted]	NR
CR, n (%)	5 (20.8)	[redacted]	[redacted]	NR
PR, n (%)	18 (75.0)	[redacted]	[redacted]	NR
Median DoR (95% CI), months	NE (42.8 to NE)	[redacted]	[redacted]	NR
DoR rate ≥12 months (95% CI)	100.0 (NE to NE)	[redacted]	[redacted]	NR
DoR rate ≥24 months (95% CI)	90.9 (50.8 to 98.7)	[redacted]	[redacted]	NR
DoR rate ≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
DoR rate ≥48 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
Patients who progressed or died, n (%)	[redacted]	[redacted]	[redacted]	NR
Median PFS, months (range)	NE (44.2 to NE)	[redacted]	[redacted]	NR
PFS rate ≥12 months (95% CI)	95.2 (70.7 to 99.3)	[redacted]	[redacted]	NR
PFS rate ≥24 months (95% CI)	95.2 (70.7 to 99.3)	[redacted]	[redacted]	NR
PFS rate ≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
PFS rate ≥48 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
Patients who died, n (%)	[redacted]		[redacted]	
Median OS, months (range)	[redacted]		[redacted]	
OS rate ≥12 months (95% CI)	[redacted]		[redacted]	
OS rate ≥24 months (95% CI)	[redacted]		[redacted]	
OS rate ≥36 months (95% CI)	[redacted]		[redacted]	

CI=confidence interval; CR=complete response; CS=company submission; DoR=duration of response; NE=not estimable; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 27 to Table 29, CS Appendix N1.2, p146, Table 71 to Table 73, Clarification Question A12

Overall, LIBRETTO-001 trial ORRs show that a high proportion of patients obtained a CR or PR to treatment (only 1 patient did not respond); [redacted].

The company highlighted (CS, p83) that Waterfall plots showing the best change in tumour size demonstrated that tumours were reduced by >25% for most patients in the systemic-therapy naïve (CS, Figure 17) and any-line populations (CS, Figure 18). Median DoR was not reached as too few patients who achieved ORR (CR or PR) subsequently progressed or died; most patients who achieved an ORR were still responding to treatment (as shown by the DoR rates in Table 18).

Investigator-assessed results

Investigator-assessed tumour response and disease progression results were provided for the systemic therapy-naïve population (CS, Appendix N1.2). There was some variability between IRC-assessed and investigator-assessed results for [redacted]. However, this may be due to the relatively small sample sizes of patients in the systemic therapy-naïve and any-line populations.

Subgroup analysis results

The company presented (CS, Section 2.7.2) IRC-assessed ORR and DoR subgroup analysis results for systemic therapy-naïve patients by type of *RET* alteration, type of molecular assay used, and the number and types of prior therapy. The systemic therapy-naïve subgroup populations were small (for some subgroups, [redacted]) and, consequently, confidence intervals were often wide. Across subgroups, results appear to be broadly consistent with the overall systemic therapy-naïve population results. For most subgroups, DoR was [redacted].

3.8 *Patient reported outcomes from the selpercatinib trials included in the CS*

3.8.1 LIBRETTO-001 trial HRQoL results: *RET*-mutant MTC

The company provided (CS, Section 2.6.1, p79) HRQoL data for cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC from the most recent LIBRETTO-001 trial DCO (13 January 2023).

HRQoL data were collected during the LIBRETTO-001 trial using the European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30 (EORTC QLQ-C30) and, for *RET*-mutant MTC patients only, a modified version of the Systemic Treatment-

Induced Diarrhoea Assessment Tool (mSTIDAT). HRQoL data were collected at baseline, at Cycle 3 and then every 8 weeks up to Cycle 13; HRQoL data were thereafter collected every 12 weeks. The company provided HRQoL data for Cycle 3, Cycle 5, Cycle 7 and Cycle 9 (CS, Table 24 and Table 25). LIBRETTO-001 trial HRQoL data were not used to inform the company cost effectiveness analysis.

EORTC QLQ-C30

Data were available for [redacted]/143 ([redacted]) cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC who had completed a full EORTC-QLQ-C30 baseline assessment and at least one full post-baseline EORTC-QLQ-C30 assessment (CS, p80).

At Cycle 9, data were available for [redacted] patients (CS, Table 25). More ([redacted]; [redacted]) patients reported a clinically meaningful improvement in global health status/QoL subscale score (≥10-point increase from baseline score) than reported a clinically meaningful worsening in global health status/QoL subscale score (≥10-point decrease from baseline score; [redacted], [redacted] patients); however, most ([redacted], [redacted]) patients had a stable global health status/QoL subscale score (<10-point change from baseline score). Approximately [redacted] of patients reported improved fatigue and diarrhoea, while approximately [redacted] of patients reported worsened fatigue and constipation (CS, Table 24).

mSTIDAT bowel diaries

The company provided mSTIDAT data (CS, Appendix N.2). Data were available for [redacted]/143 ([redacted]) cabozantinib/vandetanib-naïve patients who had completed a baseline mSTIDAT assessment and at least one post-baseline mSTIDAT assessment.

Most patients ([redacted]; [redacted]) reported having diarrhoea at baseline. At Cycle 3, [redacted] ([redacted]) patients reported having mild to moderate diarrhoea, the remaining [redacted] ([redacted]) patients reported having no diarrhoea. At Cycle 7, [redacted] ([redacted]) patients reported having mild to moderate diarrhoea and [redacted] ([redacted]) patients reported having no diarrhoea. The mean score for all six mSTIDAT items improved between baseline and Cycle 9.

3.8.2 LIBRETTO-531 trial HRQoL results: *RET*-mutant MTC

LIBRETTO-531 trial HRQoL data were not available at the time of the appraisal (Clarification Question A15).

3.8.3 LIBRETTO-001 trial HRQoL results: *RET* fusion-positive TC

EORTC QLQ-C30

Data were available for [redacted]/24 ([redacted]) systemic therapy-naïve patients with *RET* fusion-positive TC.

At Cycle 9, more ([redacted]; [redacted]) patients reported a clinically meaningful improvement in global health status/QoL subscale score than reported a clinically meaningful worsening ([redacted]; [redacted]) (CS, Table 31); however, most ([redacted]; [redacted]) patients had a stable global health status/QoL subscale score. Approximately [redacted] of patients reported improved fatigue, pain and dyspnoea. Approximately [redacted] of patients reported worsened fatigue, while [redacted] reported worsened constipation and diarrhoea (CS, Table 30).

3.9 *Safety and tolerability results from the selpercatinib trials included in the CS*

LIBRETTO-001 trial and LIBRETTO-531 trial safety and tolerability results are provided in the CS (CS, Section B.2.10, pp124-132 and Appendix M.3). LIBRETTO-001 trial selpercatinib AE data are available for:

- all patients regardless of type of cancer or line of treatment (n=837)
- patients with any-line *RET*-mutant MTC (n=324)
- patients with any-line *RET* fusion-positive TC (n=66).

In the LIBRETTO-001 trial, mean time on treatment with selpercatinib was [redacted] months for patients with *RET*-mutant MTC and [redacted] months for patients with *RET* fusion-positive TC. In the LIBRETTO-531 trial, median duration of treatment for patients treated with selpercatinib, cabozantinib and vandetanib were 14.9 months, 6.5 months and 18.5 months respectively.

The LIBRETTO-001 trial and LIBRETTO-531 trial safety analysis results showed that:

- any grade treatment-emergent AEs affecting [redacted] of LIBRETTO-001 patients with *RET*-mutant MTC (n=324) or *RET* fusion-positive TC (n=66) treated with selpercatinib were oedema, fatigue, diarrhoea, hypertension and dry mouth (CS, p127)
- common treatment-emergent AEs and AEs of special interest (AESIs) experienced by patients treated with selpercatinib were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication (CS, p124 and p134); dose reductions due to AEs were reported for:
    - [redacted] patients with *RET*-mutant MTC and [redacted] patients with *RET* fusion-positive TC in the LIBRETTO-001 trial (CS, Table 48)
    - 75/193 (38.9%) patients with *RET*-mutant MTC in the selpercatinib arm of the LIBRETTO-531 trial
- in the LIBRETTO-531 trial, the safety profile of selpercatinib was better than the safety profile of physician's choice (cabozantinib or vandetanib; CS, Appendix M.3, p140).

The EAG notes that there were some differences in frequencies of AEs across the selpercatinib trials (see Appendix 3, Section 8.3). In all three selpercatinib trials:

- very common (as defined in the summary of product characteristics [SmPC] as ≥10%) any-grade AESIs for patients treated with selpercatinib were hypertension, alanine aminotransferase (ALT) increases, aspartate transaminase increases and electrocardiogram QT prolongation
- the only very common Grade ≥3 AESI for patients with *RET*-mutant MTC or *RET* fusion-positive TC was hypertension; clinical advice to the EAG is that hypertension is easily managed in NHS clinical practice
- ALT increase was a very common Grade ≥3 AESI in the LIBRETTO-001 safety population (across all cancer types).

Clinical advice to the EAG is that differences in AE frequencies for patients treated with selpercatinib across trials may be attributable to differences in patient characteristics, perhaps most obviously, line of treatment. Focusing on LIBRETTO-001 trial any-line patient safety data may therefore over-estimate safety concerns for systemic therapy-naïve patients.

Clinical advice to the EAG agrees with the company (CS, p134) that selpercatinib is well tolerated for patients with *RET*-mutant MTC and for patients with *RET* fusion-positive TC and, for patients with *RET*-mutant MTC, selpercatinib is better tolerated than cabozantinib. As the LIBRETTO-531 trial *only* included cabozantinib/vandetanib-naïve patients, AE data from this trial may be the most applicable to this appraisal for patients with untreated MTC. However, there were only 98 patients in the control arm of this trial, not all of whom received the comparator of interest (cabozantinib) and most data were reported for the control arm as a whole, rather than separately for cabozantinib and vandetanib. For patients with *RET* fusion-positive TC, there is no direct comparative safety evidence and few patients (*RET* fusion-positive TC safety analysis set: n=66) have been treated with selpercatinib; of the treated patients, most (41/66, 62.1%) were not systemic therapy-naïve patients.

3.10 *Critique of the indirect evidence: RET-mutant MTC population*

For patients with *RET*-mutant MTC, the relevant comparators to selpercatinib are cabozantinib and BSC. The company's SLR did not identify any head-to-head trials investigating the efficacy of selpercatinib versus either of these comparators. The LIBRETTO-531 trial provides relevant evidence; however, publication was not identified by the company searches as it was only published 9 days prior to the company evidence submission to NICE. The company considered (CS, p102) that although the LIBRETTO-531 trial investigates the efficacy of selpercatinib versus cabozantinib or vandetanib, the LIBRETTO-531 trial[32] data follow-up is too short to inform a useful comparative (efficacy or cost effectiveness) analysis. The company therefore conducted indirect comparisons to estimate the comparative efficacy of treatment

with selpercatinib versus cabozantinib and versus BSC. The company conducted PFS and OS indirect comparisons.

3.10.1 Trials included in the indirect comparisons: RET-mutant MTC population

The company's SLR identified only one relevant trial, the EXAM trial, that investigated treatment with cabozantinib versus placebo in an advanced MTC population. The EXAM trial was an international, double-blind, phase III RCT that enrolled patients with locally advanced or metastatic MTC. In total, 219 patients were randomised to treatment with cabozantinib and 111 patients were randomised to placebo. Patients randomised to placebo were not permitted to crossover to cabozantinib treatment. The company considered that the EXAM trial placebo arm was a suitable proxy for BSC; clinical advice to the EAG is that this assumption is reasonable for PFS but not for OS as, in the EXAM trial, 49.5% of placebo arm patients subsequently received systemic therapies.

While positive *RET* mutation status was not required for enrolment in the EXAM trial, the following *RET* mutation status data were available:

- *RET*-mutant MTC: baseline characteristics (for the cabozantinib arm) and PFS results (both arms)
- *RET* M918T mutation-positive subgroup (not *RET*-mutant MTC patients): OS results (both arms).

RET mutation status efficacy subgroup data were included in the indirect comparisons.

The LIBRETTO-001 and EXAM trials included systemic therapy-naïve and systemic therapy-experienced patients. The company explained (CS, p102) that as clinical effectiveness results from the EXAM trial were only reported for the any-line population, LIBRETTO-001 trial any-line MTC population data were used in the indirect comparisons to 'more closely match the characteristics of the EXAM trial population'. The EAG notes that all patients in the EXAM trial were cabozantinib-naive, so using data for the cabozantinib/vandetanib-naive population from the LIBRETTO-001 trial in the MAICs would have improved comparability of data from the two trials and would have been informative.

3.10.2 Patient characteristics of trials included in the indirect comparisons: *RET*-mutant MTC population

Key characteristics of the patients with MTC in the LIBRETTO-001 and EXAM trials are presented in Table 19.

Table 19 LIBRETTO-001 and EXAM trials: MTC, patient baseline characteristics

Characteristic	LIBRETTO-001	EXAM		
	Selpercatinib	Cabozantinib		Placebo
	RET-mutant MTC any-line (n=295)	*RET*-mutant MTC[a] (n=107)	Any *RET* status MTC (n=219)	Any *RET* status MTC (n=111)
Age, median (range) years	58 (15 to 90)	55 (20 to 86)	55 (20 to 86)	55 (21 to 79)
≥65 years, n (%)	[redacted]	23 (21.5)	47 (21.5)	25 (22.5)
Male, n (%)	180 (61.0)	73 (68.2)	151 (68.9)	70 (63.1)
White, n (%)	[redacted]	NR	NR	NR
Asian, n (%)	[redacted]	NR	NR	NR
ECOG PS≥1, n (%)	184 (62.4)	41 (38.3)	95 (43.4)	55 (49.5)
Stage IV disease, n (%)	[redacted]	NR	NR	NR
RET M918T mutation-positive, n (%)	[redacted][b]	NR (74.6)[c]	75 (52.8)[d]	43 (58.9)[d]
Median (range) time from initial diagnosis, months	[redacted]	NR	NR	NR
Median (range) time from diagnosis of metastatic disease, months[e]	[redacted]	NR	NR	NR
Patients with measurable disease, n (%)[f]	[redacted]	101 (94.4)	208 (95.0)	NR
Received prior kinase inhibitor, n (%)[g]	[redacted]	23 (21.5)	44 (20.1)	24 (21.6)

[a] Data were only available for patients with *RET*-mutant MTC in the cabozantinib arm, not the placebo arm
[b] Reported as a proportion of the *RET*-mutant MTC efficacy analysis set (n=[redacted]) patients as RET mutation status data were unavailable for the any-line *RET*-mutant MTC population (n=295)
[c] Percentage from CS, Table 39. It is unclear to the EAG if *RET* M918T mutation status was known for all 107 patients with *RET*-mutant MTC
[d] Reported for patients with known RET mutation status; cabozantinib n=142, placebo n=73
[e] Median (range) of [redacted] any-line patients in LIBRETTO-001 trial
[f] Assessed by Independent Radiology Committee in EXAM trial, by Investigator in LIBRETTO-001 trial
[g] Prior tyrosine kinase inhibitor reported in EXAM trial and prior multi-kinase inhibitor reported in LIBRETTO-001 trial
CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; MTC=medullary thyroid cancer; NR=not reported; RET=rearranged during transfection
Source: CS, Table 7 to Table 10, Table 13; Elisei 2013[36]

The LIBRETTO-001 and EXAM trial baseline patient characteristics that were most notably different were:

- the LIBRETTO-001 trial any-line population included a higher proportion of patients with ECOG PS≥1 than the EXAM trial
- the LIBRETTO-001 trial any-line population included a [redacted] proportion of patients who had received a prior kinase inhibitor than the EXAM trial.

3.10.3 Quality assessment of trials included in the indirect comparisons: *RET*-mutant MTC population

The company conducted quality assessments of the EXAM trial (CS, Appendix D.3, Table 23) using the NICE process and methods [PMG6] methodology checklist for RCTs[40] which is consistent with the quality assessment checklist for clinical trials[49] devised by the Centre for Reviews and Dissemination (CRD) at the University of York. The company's assessments and EAG comments are presented in Table 20.

The EAG considers that the EXAM trial has low risk of bias and was of good methodological quality but highlights that adequate information about randomisation/allocation is lacking.

Table 20 EXAM trial: quality assessment

Parameter	EXAM trial	
	Company response	EAG assessment and comment
Was randomisation carried out appropriately?	Yes Patients were randomly assigned in a 2:1 ratio to receive cabozantinib or placebo in a double-blind fashion and were stratified by age and prior TKI treatment	Unclear The method of randomisation was not reported, e.g., random numbers generated by computer
Was the concealment of treatment allocation adequate?	Unclear Methods to conceal treatment allocation were not reported	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes Baseline characteristics were balanced between treatment arms	Differences of 5% to 7% between treatment arms for *RET* M918T mutation status, ECOG PS, patients with prior systemic therapy for MTC and patients with liver metastases
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes This was a double-blind study. ClinicalTrials.gov states that the patients, care providers, the investigator, and the outcomes assessor were blind to treatment allocation	Yes
Were there any unexpected imbalances in dropouts between groups?	Yes The proportion of patients discontinuing early from the study was comparable in both treatment groups and a CONSORT diagram outlines this. 2% did not receive treatment in both arms but there was more disease progression in the placebo arm (60%) compared with the cabozantinib arm (26%)	Yes A higher proportion of patients in the placebo arm discontinued treatment (86%) than in cabozantinib arm (55%) and a higher proportion of patients who discontinued treatment in the placebo arm did so at their own request (12%) than in the cabozantinib arm (4%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No Authors reported all outcomes listed in the methods section	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate, and were appropriate methods used to account for missing data?	Yes ITT analysis was performed for PFS and OS. For tumour response, only patients with measurable disease at baseline were included in the analysis	Yes

CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; ITT=intention-to-treat; MAIC=matching-adjusted indirect comparison; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor
Source: CS, Appendix D, Table 23; Elisei 2013[36]

3.10.4 Indirect comparison methodology: *RET*-mutant MTC population

The LIBRETTO-001 trial is a single-arm study and therefore the company was unable to perform network meta-analyses or indirect comparisons as these methods rely on trials

sharing a common comparator. Instead, the company conducted unanchored MAICs; these included any-line data from the LIBRETTO-001 and EXAM trials.

Unanchored MAICs allow adjustment for potential bias due to differences in prognostic variables and treatment effect modifiers across trials. Unanchored MAICs use individual patient-level data from a treatment arm in one trial (in this case, the LIBRETTO-001 trial) and match these data to summary-level baseline characteristics of a treatment arm in another trial (in this case, the EXAM trial). For PFS, the company matched selpercatinib data from the any-line *RET*-mutant MTC LIBRETTO-001 trial patient population with cabozantinib or placebo data from the any-line *RET*-mutant EXAM trial patient population. For OS, the company matched data from the any-line *RET*-mutant MTC LIBRETTO-001 trial patient population with data from the any-line *RET* M918T mutation-positive EXAM trial patient population.

Unanchored MAICs should adjust for all prognostic factors and effect modifiers. Prognostic factors and effect modifiers for patients with MTC were identified as part of the company's SLR (CS, Appendix D, Table 20). Expert advice to the company was that the company's list of prognostic factors and effect modifiers was comprehensive.[23]

Many of the identified prognostic factors and effect modifiers were not reported in the LIBRETTO-001 trial or were not reported in the EXAM trial and so could not be adjusted for in the MAICs (Appendix 4, Section 8.4). As it has not been possible to compare LIBRETTO-001 trial and EXAM trial prognostic factor and effect modifier distributions, it is not known whether imbalances in these patient characteristics introduce bias into the MAIC results.

The prognostic factors and effect modifiers that the company adjusted for in the MAICs were:

- age
- weight
- ECOG performance score
- sex
- smoking status
- RET M918T mutation status
- prior MKI treatment.

Weight, sex, smoking status and prior MKI treatment were not identified as prognostic factors and effect modifiers by the company's SLR. Clinical advice to the company (Clarification Question A17) was that sex and smoking status are prognostic factors. The company considered (Clarification Question A17) that published literature supports that sex and smoking status, respectively, are prognostic factors for survival in thyroid cancer and in the

general population. Clinical advice to the EAG is that the prognostic factors and effect modifiers adjusted for in the MAICs were appropriate.

LIBRETTO-001 trial patients were assigned weights to match the baseline characteristics of the weighted any-line *RET*-mutant MTC LIBRETTO-001 trial patient population with the baseline characteristics of the EXAM trial *RET*-mutant MTC population. EXAM trial *RET*-mutant subgroup baseline characteristics were only available for the cabozantinib arm (Section 3.10.1). Therefore, when the company performed MAICs including LIBRETTO-001 trial selpercatinib data and EXAM trial placebo data, the company assumed that EXAM trial placebo arm *RET*-mutant patient baseline characteristics were similar to EXAM trial cabozantinib arm RET-mutant patient baseline characteristics. The EAG considers that, in the absence of an alternative approach, the company's assumption is reasonable, because, for patients with any *RET mutation* status, baseline characteristics in both EXAM trial arms are similar (Table 19).

OS results were only available for the EXAM trial *RET* M918T mutation-positive subgroup. The company approach assumes that EXAM trial baseline characteristics for patients with *RET* M918T mutation are similar to EXAM trial baseline characteristics for patients with any *RET* mutation. Clinical advice to the EAG is that *RET* M918T mutation-positive patients may have a poorer prognosis and may develop metastatic disease earlier than patients with any *RET* mutation, but that there are no other specific patient characteristics that would differ between these patient groups. The EAG therefore considers the company's approach to be reasonable.

Weights were obtained from a logistic regression model that was estimated using the method of moments. For PFS, the weighted curve for the LIBRETTO-001 trial any-line *RET*-mutant MTC population was compared to the unweighted curves for the EXAM trial *RET*-mutant cabozantinib arm (n=107) or placebo arm (n=62) populations (digitised Sherman 2016[45] data). A weighted Cox proportional hazards (PH) model was used to generate a hazard ratio (HR) and corresponding 95% confidence interval (CI); treatment indicator was the only covariate.

For OS, the weighted curve for the LIBRETTO-001 trial any-line *RET*-mutant MTC population was compared with the unweighted EXAM trial *RET* M918T mutation-positive cabozantinib arm (n=81) and placebo arm (n=45) curves (digitised Schlumberger 2017[46] data). A weighted Cox PH model was used to generate HRs and corresponding 95% CIs; treatment indicator and *RET* M918T mutation status were the two covariates. It is not clear how the company was able to include *RET* M918T mutation status as a covariate in the Cox PH model as *RET* M918T

mutation status data were not available for the LIBRETTO-001 trial any-line *RET*-mutant MTC population (CS, Table 13 footnote).

3.10.5 Indirect comparison results: *RET*-mutant MTC population

A summary of the baseline characteristics of the LIBRETTO-001 trial any-line *RET*-mutant MTC population (prior to, and after, matching), and the EXAM trial *RET*-mutant MTC population (cabozantinib arm only) is provided in Table 21. After applying MAIC weights to LIBRETTO-001 trial[31] data, all matched-adjusted baseline characteristics were exactly balanced between the two study populations. After weighting, the effective sample size for the LIBRETTO-001 trial any-line *RET*-mutant MTC population was 157.

Table 21 LIBRETTO-001 trial any-line *RET*-mutant MTC population (prior to, and after, matching) and the EXAM trial *RET*-mutant population (cabozantinib arm only): patient baseline characteristics

	LIBRETTO-001 any-line *RET*-mutant MTC patients		EXAM *RET*-mutant cabozantinib (n=107)
	Before matching (n=295)	After matching (N_{eff}=[redacted])	
Age, mean (SD)	[redacted]	[redacted]	55.0 (15.2)
Weight (kg), mean (SD)	[redacted]	[redacted]	74.0 (21.0)
ECOG PS 0 (%)	37.6	[redacted]	61.7
Sex (% male)	61.0	[redacted]	68.2
Smoking (% never)	[redacted]	[redacted]	51.4
RET M918T mutation-positive (%)	[redacted]	[redacted]	74.6
Prior TKI/MKI therapy (%)	[redacted]	[redacted]	21.5

CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; MKI=multi-kinase inhibitor; MTC=medullary thyroid cancer; N_{eff}=effective sample size; *RET*=rearranged during transfection; SD=standard deviation; TKI=tyrosine kinase inhibitor
Source: CS, Table 39

The company scaled the weights; a re-scaled weight >1 means that an individual has more influence on results in the weighted population than in the original, unweighted population, and a re-scaled weight <1 means that an individual has less influence in the weighted population than in the original, unweighted population. The company then inspected the distribution of rescaled weights for extreme values (CS, Figure 27); extreme values are indicative of poor overlap between study populations in terms of the distributions of patient characteristics. The company identified no evidence of extreme weights.

Company MAIC results are presented in Table 22. For comparative purposes, the company has also presented results from unadjusted indirect comparisons. The EAG considers that it can be useful to consider unadjusted indirect comparison results as they give an indication of the impact that the company's adjustments have had on efficacy estimates. However, the EAG cautions that unadjusted indirect comparison results should not be used to inform decision

making. PFS and OS Kaplan-Meier (K-M) plots, before and after weighting, are presented in the CS (Figure 28 and Figure 29, respectively).

Table 22 Comparison of selpercatinib (LIBRETTO-001 trial), cabozantinib (EXAM trial) and BSC (EXAM trial) PFS and OS results before and after matching

	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Selpercatinib versus cabozantinib				
Unadjusted indirect comparison	[redacted]	[redacted]	[redacted]	[redacted]
MAIC	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib versus BSC				
Unadjusted indirect comparison	[redacted]	[redacted]	[redacted]	[redacted]
MAIC	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; CI=confidence intervals; CS=company submission; HR=hazard ratio; MAIC=matching-adjusted indirect comparison; MTC=medullary thyroid cancer; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection
Source: CS, Table 40

All HRs and 95% CIs suggested statistically significant treatment effects that were strongly in favour of selpercatinib. Applying the MAIC methodology led to treatment effect estimates that favoured selpercatinib over cabozantinib and BSC even more strongly than those calculated using unadjusted indirect comparison methods.

As Cox PH models were used to estimate HRs and 95% CIs, the company assessed the validity of the PH assumption for each MAIC and unadjusted indirect comparison (CS, Appendix O). The Cox PH model is only an appropriate method if the PH assumption holds, i.e., if the event hazards associated with the intervention and comparator data are proportional over time. The company considered log-cumulative hazard plots, Schoenfeld residual plots and the global Schoenfeld residuals test of proportional hazards, and concluded that, for PFS, the PH assumption appears to be violated for the comparison of selpercatinib versus BSC (MAIC and unadjusted indirect comparison). For all other indirect comparisons, the company concluded that the PH assumption was valid. The EAG agrees with the company's conclusions.

3.10.6 EAG comment on company indirect comparisons: *RET*-mutant MTC population

The EAG considers that the methods used by the company to conduct MAICs were generally appropriate. The EAG agrees with the company that data from the LIBRETTO-531 trial are immature (median PFS follow up: LIBRETTO-001, [redacted] months; LIBRETTO-531 selpercatinib arm, [redacted] months; LIBRETTO-531 physician's choice arm, [redacted] months), but considers that LIBRETTO-531 trial clinical effectiveness results are likely to be the most relevant for patients with *RET*-mutant MTC in this appraisal (see Section 2.5.3 and Section 3.3.2 of this EAG

report). The EAG notes that LIBRETTO-531 trial early clinical efficacy results are in line with company MAIC results. LIBRETTO-531 trial PFS and OS results indicate a strong treatment effect in favour of selpercatinib over physician's choice (cabozantinib or vandetanib; see Section 3.7.3 of this EAG report).

When interpreting company MAIC results, it is important to consider that:

- adjustments were not made to account for differences in all identified prognostic factors and effect modifiers (Appendix 4, Section 8.4).
- the CS did not contain any discussion about the likely amount of residual systematic error in the MAICs
- it is not known whether the lack of adjustment for all prognostic factors and effect modifiers will have introduced bias into company MAIC results, or whether any bias would favour selpercatinib or the comparators.
- EXAM trial placebo arm data are not a good proxy for BSC OS data.

An additional consideration is that the HRs and 95% CIs generated by the MAICs are estimates of the effectiveness of selpercatinib versus relevant comparators for the any-line *RET*-mutant MTC population, i.e., the EXAM trial cabozantinib arm population, 21.5% of whom had received prior MKI/TKI therapy. The MAICs do not generate results for the population that is the focus of this appraisal, i.e., systemic therapy-naïve patients with *RET*-mutant MTC.

Further, the PFS PH assumption appears to be violated for the comparison of selpercatinib versus BSC (MAIC and unadjusted indirect comparison). Therefore, the reported PFS HR may not provide an accurate numerical estimate of the comparative efficacy of selpercatinib versus BSC.

Due to the limitations of the company's MAICs, the EAG considers that the reported effect estimates may not represent the true underlying treatment effect of selpercatinib versus the relevant comparators for the systemic therapy-naïve population with *RET*-mutant positive MTC. However, the EAG also considers that the potential biases and limitations would be unlikely to change the broad conclusions that can be drawn from the company's MAICs, and that there is sufficient evidence to conclude that selpercatinib improves PFS and OS in comparison to cabozantinib and BSC for systemic therapy-naïve patents with *RET*-mutant MTC.

3.11 *Critique of the indirect evidence: RET fusion-positive TC population*

The relevant comparators to selpercatinib for patients with *RET* fusion-positive TC are lenvatinib, sorafenib and BSC. The company's SLR did not identify any head-to-head trials investigating the efficacy of selpercatinib versus any of these comparators. Therefore, the

company conducted indirect comparisons to generate estimates of the comparative efficacy of selpercatinib versus lenvatinib, versus sorafenib and versus BSC.

3.11.1 Trials included in the company indirect comparisons: *RET* fusion-positive TC population

The company identified two trials, the SELECT trial (lenvatinib versus placebo) and the DECISION trial (sorafenib versus placebo) that were considered eligible for inclusion in indirect comparisons. Both the SELECT and DECISION trials were international, double-blind, phase III RCTs that enrolled patients with radioactive iodine-refractory differentiated or poorly-differentiated thyroid cancer. The company considered that the placebo arms of the SELECT and DECISION trials were suitable proxies for BSC.

The SELECT trial only enrolled patients who had had one or no prior TKI or MKI therapy (i.e., systemic therapy-experienced and systemic therapy-naïve, respectively). The DECISION trial only enrolled patients who had received no prior targeted (including TKI or MKI) cancer therapy (i.e., systemic therapy-naïve). SELECT trial OS data were not reported separately for systemic therapy-naïve and systemic therapy-experienced patients. Therefore, the company chose to include any-line *RET* fusion-positive TC population data (i.e., not restricted by prior treatment status) from the LIBRETTO-001 trial in the indirect comparisons.

Furthermore, DECISION trial and SELECT trial clinical effectiveness results were not available for subgroups defined by *RET* fusion-positive status (*RET* fusion status was not collected as part of these trials). Therefore, the company's indirect comparisons compared any-line LIBRETTO-001 trial *RET* fusion-positive patient data with any-line SELECT trial[41] and DECISION trial[38] data from patients with unknown *RET* fusion status.

In the SELECT trial (August 2011 to October 2012), patients from 21 countries were randomly assigned 2:1 to receive lenvatinib (n=261) or placebo (n=131). In the DECISION trial (December 2009 to August 2012), patients from 18 countries were randomly assigned 1:1 to receive sorafenib (n=207) or placebo (n=210).

3.11.2 Patient characteristics of trials included in the indirect comparisons: *RET* fusion-positive TC population

Key baseline characteristics of patients in the LIBRETTO-001 trial, SELECT trial and DECISION trial are presented in Table 23.

Table 23 SELECT, DECISION and LIBRETTO-001 trials: advanced TC, patient baseline characteristics

Characteristic	LIBRETTO-001	SELECT		DECISION	
	Selpercatinib	Lenvatinib	Placebo	Sorafenib	Placebo
	RET fusion-positive any-line TC (n=65)	Any *RET* status any-line TC (n=261)	Any *RET* status any-line TC (n=131)	Any *RET* status systemic therapy-naïve[a] TC (n=207)	Any *RET* status systemic therapy-naïve[a] TC (n=210)
Age, median (range) years	59 (20 to 88)	64 (27 to 89)	61 (21 to 81)	63 (24 to 82)	63 (30 to 87)
Male, n (%)	32 (49.2)	125 (47.9)	75 (57.3)	104 (50.2)	95 (45.2)
White, n (%)	[redacted]	208 (79.7)	103 (78.6)	123 (59.4)	128 (61.0)
Asian, n (%)	[redacted]	46 (17.6)	24 (18.1)	47 (22.7)	52 (24.8)
Region, n (%)					
Europe	[redacted]	131 (50.2)	64 (48.9)	124 (59.9)	125 (59.5)
North America	[redacted]	77 (29.5)	39 (29.8)	36 (17.4)	36 (17.1)
Other	[redacted]	53 (20.3)	28 (21.4)	47 (22.7)	49 (23.3)
ECOG PS ≥1, n (%)	40 (61.5)	117 (44.8)	63 (48.1)	76 (36.7)	80 (38.1)
Stage IV disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology, n (%)					
Papillary	[redacted]	132 (50.6)	68 (51.9)	118 (57.0)	119 (56.7)
Poorly differentiated	[redacted]	28 (10.7)	19 (14.5)	24 (11.6)	16 (7.6)
Follicular, not Hürthle cell	[redacted]	53 (20.3)	22 (16.8)	13 (6.3)	19 (9.0)
Hürthle cell	[redacted]	48 (18.4)	22 (16.8)	37 (17.9)	37 (17.6)
Other	[redacted]	0	0	2 (1.0)	5 (2.4)
Missing or non-diagnosed	[redacted]	0	0	13 (6.3)	14 (6.7)
Median (range) time from initial diagnosis, months	[redacted]	66 (0.4 to 573.6)	73.9 (6.0 to 484.8)	66.2 (3.9 to 362.4)	66.9 (6.6 to 401.8)
Received prior kinase inhibitor, n (%) [b]	[redacted]	66 (25.3)	27 (20.6)	0	0

[a] Systemic therapy-naïve patients may have received radioactive iodine therapy
[b] Numbers of patients who had previously been treated with a TKI were reported in the SELECT and DECISION trials; prior treatment with an MKI was reported in the LIBRETTO-001 trial
CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; NR=not reported; RET=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 9 to Table 11 and Table 41; Fleeman 2019[50]

The LIBRETTO-001 trial any-line TC population characteristics that were most notably different from the SELECT trial and the DECISION trial population characteristics were:

- a higher proportion of patients in the LIBRETTO-001 trial any-line population had ECOG PS ≥1 than in the SELECT and DECISION trial populations
- all patients in the LIBRETTO-001 trial any-line population had *RET*-alterations but patient *RET* fusion status was unknown in the SELECT and DECISION trials
- a notably higher proportion of patients in the LIBRETTO-001 trial any-line population had papillary TC (which was expected as *RET* fusion alterations are more common for patients with papillary TC than other types of TC) than in the SELECT and DECISION trials

- the median time from initial diagnosis was [redacted] in the LIBRETTO-001 trial any-line population than in the SELECT and DECISION trial populations
- the proportion of patients in the LIBRETTO-001 trial any-line population who had received a prior MKI was [redacted] than the proportion of patients in the SELECT and DECISION trial populations who had received a prior TKI

3.11.3 Quality assessment of trials included in the indirect comparisons: *RET* fusion-positive TC population

The company conducted quality assessments of the SELECT and DECISION trials (CS, Appendix D.3, Table 23) using the NICE process and methods [PMG6] methodology checklist for RCTs[40] which is consistent with the quality assessment checklist for clinical trials[49] devised by the Centre for Reviews and Dissemination (CRD) at the University of York. The company's assessments and EAG comments are presented in Table 24. The EAG considers that the SELECT and DECISION trials were of good methodological quality and have low risk of bias.

Table 24 SELECT and DECISION trials: quality assessment

Parameter	SELECT trial		DECISION trial	
	Company response	EAG comment	Company response	EAG comment
Was randomisation carried out appropriately?	Yes Block randomisation was performed centrally by means of an interactive voice- and web-response system	Yes	Yes Patients were randomised 1:1 via an IVRS	Yes
Was the concealment of treatment allocation adequate?	Yes A central, interactive voice- and web-response system was used to allocate treatment	Yes	Yes Interactive voice- and web-response system was used	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes Baseline characteristics were balanced between treatment arms	Yes Most characteristics were balanced between treatment arms but some differences were noted[a]	Yes Baseline characteristics were balanced between treatment arms	Yes Most characteristics were balanced between treatment arms but some differences were noted[b]
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes The study was double-blind. clinicaltrials.gov states that the patients, care providers, and the investigator were blind	Yes	Yes Patients, investigators, and sponsor were blind to treatment assignment via unique drug pack numbers pre-printed onto each bottle or package and assigned to the patient via IVRS	Yes
Were there any unexpected imbalances in dropouts between groups?	No 17% of patients in the lenvatinib arm discontinued (45/261) and 3% (4/119) discontinued in the placebo arm. The reasons are outlined in the CONSORT diagram	Yes	Yes Dropouts were recorded in the CONSORT diagram. 75 discontinued sorafenib compared with only 22 in the placebo arm because of more adverse events; 31 in the sorafenib arm and 5 in the placebo arm	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No Authors reported all outcomes listed in the methods section	No	No Authors reported all outcomes listed in the methods section	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate, and were	Yes ITT analysis was performed on both primary and secondary efficacy outcomes. A per-	Yes	Yes ITT analysis was performed for PFS, OS, and TTP. ORR and DCR were analysed in patients	Yes

appropriate methods used to account for missing data?	protocol analysis was performed on PFS as the primary outcome only and yielded the same results as the ITT		who received study medication and had a baseline and a postbaseline tumour evaluation	

[a] In the SELECT trial, median time from diagnosis of differentiated TC to randomisation was shorter in the lenvatinib arm than in the placebo arm (66.0 months versus 73.9 months). Compared with the placebo arm, a smaller proportion of patients in the lenvatinib arm had metastases in the lung (86.6% versus 94.7%) or liver (16.5% versus 21.4%).
[b] In the DECISION trial, a higher proportion of patients in the sorafenib arm had metastases in the lymph node (54.6%) or pleura (19.3%) than in the placebo arm (48.1% and 11.4% respectively).
CS=company submission; DCR=disease control rate; ITT=intention-to-treat; IVRS=interactive voice response system; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; TC=thyroid cancer originating in the follicular cells; TTP=time to progression
Source: CS, Appendix D, Table 23

3.11.4 Indirect comparison methodology: RET fusion-positive TC population

As the LIBRETTO-001 trial is a single arm study, the company was unable to perform network meta-analyses or indirect comparisons, methods that rely on trials sharing a common comparator. Instead, the company performed naïve, unadjusted indirect comparisons, i.e., no adjustments were made for prognostic factors or effect modifiers that may be distributed differently between the included trials. The company considered that performing a MAIC was not feasible due to the small size of the relevant LIBRETTO-001 trial population (any-line *RET* fusion-positive TC population: n=65). As performing a MAIC would reduce the effective sample size of the LIBRETTO-001 trial any-line *RET* fusion-positive TC trial further, the EAG agrees with the company that results from a MAIC for the *RET* fusion-positive TC population would not be informative.

The company compared LIBRETTO-001 trial[31] data with SELECT trial[37,41] data to obtain efficacy estimates for the comparison of selpercatinib versus lenvatinib and versus BSC and compared LIBRETTO-001 trial[31] data with DECISION trial[38] data to obtain efficacy estimates for the comparison of selpercatinib versus sorafenib and versus BSC.

Following disease progression, patients in the placebo arms of the SELECT and DECISION trials were permitted to crossover to receive treatment with lenvatinib or sorafenib, respectively. In the SELECT trial, 87.8% of eligible patients crossed over to receive open-label lenvatinib, and in the DECISION trial, 71.4% of eligible patients crossed over to receive open-label sorafenib. The company adjusted SELECT trial K-M OS curves to account for treatment crossover using the RPSFT method. Only DECISION trial unadjusted K-M curves are available; DECISION trial crossover-adjusted HRs and 95% CIs were available, but the company was unable to conduct the indirect comparisons without access to crossover-adjusted K-M curves. The company therefore decided not to compare the LIBRETTO-001 trial OS selpercatinib data with DECISION trial placebo arm OS data, due to the potential confounding introduced by crossover.

The company compared individual-level patient data (IPD) from the LIBRETTO-001 trial to (digitised) published SELECT and DECISION trial K-M curves. The company performed Cox PH regressions to estimate HRs and 95% CIs for selpercatinib versus the comparators (lenvatinib, sorafenib, and placebo), and non-parametric log-rank tests to evaluate statistical significance.

3.11.5 Indirect comparison results: *RET* fusion-positive TC population

Comparisons of PFS and OS data from the LIBRETTO-001, SELECT and DECISION trials are available in the CS (Table 42 and Table 44). Results from the company's unadjusted indirect comparisons are provided in Table 25.

Table 25 Company PFS and OS unadjusted indirect comparison results: *RET* fusion-positive TC population

Treatment comparison	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
LIBRETTO-001 vs SELECT				
Selpercatinib vs lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
LIBRETTO-001 vs DECISION				
Selpercatinib vs sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib vs BSC	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; CI=confidence interval; CS=company submission; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; NA=not analysed (due to crossover-adjusted data not reported); *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 43 and Table 45

PFS and OS unadjusted indirect comparison results favoured selpercatinib over the relevant comparators. However, unadjusted indirect comparison results are highly susceptible to bias, and the EAG considers that the p-values presented in Table 25 should not be used to infer statistical significance.

3.11.6 EAG comment on the indirect comparisons: *RET* fusion-positive TC population

The EAG is unaware of any studies in addition to those identified by the company that could have been used to inform comparative efficacy estimates for selpercatinib versus lenvatinib, selpercatinib versus sorafenib or selpercatinib versus BSC. The EAG therefore agrees with the company that it was not possible to perform network meta-analyses or adjusted indirect comparisons, methods that rely on trials sharing a common comparator. Further, the EAG considers that performing MAICs for the *RET* fusion-positive TC population would have been non-informative due to the small size of the LIBRETTO-001 trial RET fusion-positive TC population. The EAG is not aware of any methods that could have been used to generate robust estimates of comparative efficacy for the TC population.

Results from unadjusted indirect comparisons are highly susceptible to bias. An unadjusted indirect comparison does not account for any differences in trial or patient characteristics between included trials. The key differences between the LIBRETTO-001, SELECT and DECISION trials are outlined in Section 3.11.1 and Section 3.11.2. In addition to these differences, median PFS follow-up differed considerably between the LIBRETTO-001 trial,

SELECT trial and DECISION trial (CS, Table 42), and median OS follow-up differed considerably between the LIBRETTO-001 and DECISION trials (CS, Table 44); differences in follow-up limit the comparability of trial data.

The company included data from the LIBRETTO-001 trial any-line *RET* fusion-positive TC population in all unadjusted indirect comparisons. The EAG acknowledges that OS data were not available for the SELECT trial systemic therapy-naïve population. However, it would have been possible to perform a PFS unadjusted indirect comparison using LIBRETTO-001 trial systemic therapy-naïve population data and SELECT trial systemic therapy-naïve population data (available from Schlumberger 2015,[37] supplementary material). It would also have been possible to perform unadjusted PFS and OS indirect comparisons using LIBRETTO-001 trial[31] systemic therapy-naïve population data and DECISION trial[38] data (the DECISION trial only enrolled patients who had not received prior targeted cancer therapy). Incorporating LIBRETTO-001 trial[31] systemic therapy-naïve population data in unadjusted indirect comparisons would have improved the comparability of patient populations, improved the applicability of the unadjusted indirect comparison results to the target patient population, and reduced the potential for bias from confounding factors. However, the LIBRETTO-001 trial systemic therapy-naïve *RET* fusion-positive TC population was very small ([redacted]), and effect estimates from an unadjusted indirect comparison incorporating data from this subgroup would have been highly uncertain.

The company stated (CS, p121), that DECISION trial sorafenib OS data were associated with "clinical plausibility concerns" and concluded that "ITC results for OS between selpercatinib and sorafenib are associated with high levels of uncertainty and must be interpreted with caution". The EAG acknowledges that the risk profiles of the SELECT and DECISION trial placebo arms have been deemed to be non-comparable in a previous Multiple Technology Appraisal (MTA) (TA535),[25] and it is therefore likely that there are fundamental differences between the SELECT and DECISION trial populations. The EAG considers that results from the unadjusted indirect comparisons that include DECISION trial[38] data are no more susceptible to bias due to clinical implausibility than results from unadjusted indirect comparisons including SELECT trial[37,41] data.

In the lenvatinib and sorafenib MTA (TA535),[41] the Assessment Group considered that the placebo arms of both the SELECT and DECISION trials could be considered proxies for BSC. It is not known whether the BSC provided in the SELECT and DECISION trials were similar to BSC provided in NHS clinical practice; however, it is known that palliative radiotherapy was only permitted in the DECISION trial. Rates of palliative radiotherapy were relatively low (sorafenib: 10.6%; placebo: 21.4%). Clinical advice to the EAG is that, in NHS clinical practice,

approximately 20% to 25% % of patients with TC receive palliative radiotherapy. In addition, clinical advice to the EAG is that SELECT (and DECISION) trial placebo arm data are not good proxies for BSC OS data. The company states (CS, p113) that SELECT trial placebo arm data were selected to represent the most appropriate proxy for BSC as the SELECT trial placebo arm population was slightly larger population (n=261) than the DECISION trial placebo arm population (n=207). However, the EAG highlights that the numbers provided by the company are for the lenvatinib and sorafenib arms of the SELECT and DECISION trials, respectively; the SELECT trial placebo arm included fewer patients (n=131) than the DECISION trial (n=210).

As Cox PH models were used to estimate HRs and 95% CIs, the company assessed the validity of the PH assumption for each unadjusted indirect comparison (CS, Appendix O). The company considered log-cumulative hazard plots, Schoenfeld residual plots and the global Schoenfeld residuals test of proportional hazards, and concluded that, for selpercatinib versus BSC (SELECT trial placebo arm data), the PH assumption appears to be violated for both OS and PFS. The EAG agrees with this conclusion. The EAG also considers that the PH assumption appears to be violated for the comparison of selpercatinib versus sorafenib OS data. Therefore, the reported HRs for selpercatinib versus BSC (SELECT trial placebo arm PFS and OS data) and for selpercatinib versus sorafenib (OS data) may not provide accurate numerical estimates of comparative efficacy.

Overall, the EAG considers the company's unadjusted indirect comparison results are highly uncertain, and that the relative efficacy of selpercatinib versus lenvatinib, selpercatinib versus sorafenib, and selpercatinib versus BSC remain unknown.

3.12 *Patient reported outcomes from the comparator trials included in the CS*

3.12.1 Trials included in the CS HRQoL results: *RET*-mutant MTC population

In the EXAM trial, HRQoL data were collected using the MD Anderson Symptom Inventory (MDASI) thyroid module.[51] HRQoL results were not reported in the EXAM trial publications identified by the company SLR. However, in the TA516 Assessment Group (AG) report,[52] the AG reported that HRQoL data were available from the EXAM trial CSR and that there were no differences between treatment arms at follow-up; however, statistical testing was not performed. Clinical advice to the AG[52] (and to the EAG for this appraisal) was that the MDASI thyroid module may not capture symptomatic benefit from improved PFS and/or objective response rate. The EAG notes that EXAM trial HRQoL results were only reported for the any-line population.

3.12.2 Trials included in the CS HRQoL results: *RET* fusion-positive TC population

HRQoL data were not collected during the randomised phase of the SELECT trial.

In the DECISION trial, HRQoL data were collected using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire,[53] EuroQol-5 Dimensions three-level version (EQ-5D-3L) and the EuroQol-5 Dimensions (EQ-5D) visual analogue scale (VAS).[54] HRQoL results were reported in a conference abstract by Schlumberger 2013[47] and were provided by the company for TA535.[41] The EAG notes that the HRQoL results were reported for systemic therapy-naïve patients with advanced TC and unknown *RET* fusion status.

At the first HRQoL assessment (Cycle 2, Day 1), patients in the sorafenib arm reported a clinically meaningful worsening in FACT-G total score (change in score between 3 and 7 points) whereas the mean patient score in placebo arm remained very similar to baseline. It was reported in Schlumberger 2013 that the scores in the sorafenib and placebo arms at subsequent assessments remained similar to the scores at the first assessment. A mixed linear model estimated a clinically meaningful difference between arms in favour of the placebo arm. In TA535,[41] the company considered that the clinically meaningful difference was due to AEs associated with sorafenib and noted that in response to the FACT-G physical well-being domain question 'I am bothered by side effects', the proportion of patients in the sorafenib arm who reported 'quite a bit' or 'very much' increased from 1.5% at Cycle 1 to 29.6% at Cycle 2, however, the proportion of patients decreased to 16.8% by Cycle 6 and 8.0% by Cycle 13.

Similarly, at the first HRQoL assessment (Cycle 2, Day 1), EQ-5D index and VAS scores were lower in the sorafenib arm than in the placebo arm. The between-arm differences were statistically significant ($p<0.0001$ for both EQ-5D index and VAS), however, the treatment effects were of small magnitude and did not reach the threshold for a clinically meaningful difference (change of 0.10 points on the EQ-5D index and a change of at ≥7 points on the VAS).

3.13 *Safety and tolerability results from the comparator trials*

In the CS, safety and tolerability results are only presented from the LIBRETTO-001 and LIBRETTO-531 trials. To compare the safety of selpercatinib versus cabozantinib, versus lenvatinib and versus sorafenib, the EAG has reviewed safety data from the EXAM, SELECT and DECISION trials (Appendix 5, Section 8.5, Table 71 and Table 72). The EAG naïve comparisons show that:

- as with selpercatinib, nearly all patients in the EXAM, SELECT and DECISION trials reported an AE, including patients in the placebo arms; AEs in the placebo arms may be the result of treatment with BSC or reflect symptoms of thyroid cancer such as diarrhoea and fatigue
- the incidence of Grade ≥3 AEs for patients treated with selpercatinib was more similar to EXAM, SELECT and DECISION trial placebo arm incidences than to EXAM, SELECT and DECISION trial active treatment arm incidences
- as with patients treated with selpercatinib, diarrhoea and fatigue were very common for all patients in all trials, regardless of whether they received an active treatment or placebo; these are AEs that specifically affect the HRQoL of patients with MTC and/or TC, as they are symptoms of thyroid cancer (see Section 3.9 of this EAG report)
- as with selpercatinib, hypertension was a very common AE for patients treated with cabozantinib, lenvatinib and sorafenib
- unlike for patients treated with selpercatinib, weight-loss and PPE syndrome were very common AEs for patients treated with cabozantinib, lenvatinib and sorafenib.

Overall, clinical advice to the EAG is that, based on the evidence presented in the CS, when compared with other relevant kinase inhibitors (cabozantinib, lenvatinib and sorafenib), the safety profile of selpercatinib appears favourable. The favourable safety profile of selpercatinib versus cabozantinib is further supported by the direct evidence available from the LIBRETTO-531 trial (Section 3.9).

3.14 *EAG summary of the clinical effectiveness section*

The company provided evidence from one single-arm trial (the LIBRETTO-001 trial, selpercatinib) and one RCT (the LIBRETTO-531 trial, selpercatinib versus physician's choice [cabozantinib or vandetanib]). The EAG considers that the LIBRETTO-001 trial is a well conducted trial that enrolled any-line patients with *RET*-mutant MTC or *RET* fusion-positive TC. The LIBRETTO-531 trial is a well-conducted RCT with low risk of bias that enrolled cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC.

LIBRETTO-001 and LIBRETTO-531 trial populations

Clinical advice to the EAG is that cabozantinib/vandetanib-naïve LIBRETTO-001 and LIBRETTO-531 trial patients with *RET*-mutant MTC are representative of NHS patients with untreated advanced *RET*-mutant MTC. In the LIBRETTO-001 trial, 143/295 (48.5%) patients with *RET*-mutant MTC were cabozantinib/vandetanib-naïve.

Clinical advice to the EAG is that systemic therapy-naïve LIBRETTO-001 trial patients with *RET* fusion-positive TC are representative of NHS patients with untreated advanced *RET* fusion-positive TC. However, the LIBRETTO-001 trial only includes a small proportion of

patients with advanced *RET* fusion-positive TC (systemic therapy-naive patients with *RET* fusion-positive TC: n=24; any-line patients with *RET* fusion-positive TC: n=65).

Clinical effectiveness evidence for patients with *RET*-mutant MTC aged 12 to 18 years treated with selpercatinib is limited (LIBRETTO-001 trial: [redacted]; LIBRETTO-531 trial: n=1). There is no clinical effectiveness evidence for patients with *RET* fusion-positive TC aged 12 to 18 years treated with selpercatinib. Clinical advice to the EAG is that patients aged 12 to 18 years who have thyroid cancer with *RET* alterations are expected to have the same clinical response to therapies as patients aged ≥18 years.

***RET*-mutant MTC clinical efficacy evidence**

Clinical efficacy evidence for the comparison of selpercatinib versus cabozantinib and versus BSC for any-line patients with *RET*-mutant MTC was provided by company MAICs. All HRs and 95% CIs suggested statistically significant treatment effects that strongly favoured selpercatinib versus cabozantinib and versus BSC. The company MAIC results are uncertain (MAICs were unanchored, did not adjust for all identified prognostic factors and effect modifiers and included patients with any-line *RET*-mutant MTC and EXAM trial placebo arm data are not a good proxy for BSC OS data).

The EAG considers that the LIBRETTO-531 trial provides the most relevant evidence for this appraisal as it provides direct evidence for the comparison of selpercatinib versus cabozantinib (relevant comparator) and includes the patient population that is the focus of this appraisal. However, the EAG acknowledges that the LIBRETTO-001 trial follow-up is longer than the LIBRETTO-531 trial follow-up (only interim LIBRETTO-531 trial results are currently available) and the LIBRETTO-531 trial OS results are confounded by crossover. The LIBRETTO-531 trial interim results (selpercatinib improved PFS and OS versus cabozantinib) are in line with company MAIC results.

The EAG considers that there is sufficient evidence to suggest that selpercatinib improves PFS and OS versus cabozantinib and versus BSC for cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC.

***RET* fusion-positive TC clinical efficacy evidence**

Clinical efficacy evidence for the comparison of selpercatinib versus lenvatinib, versus sorafenib and versus BSC for systemic therapy-naïve patients with *RET* fusion-positive TC is only available from company naïve, unadjusted indirect treatment comparisons. Based on clinical advice, the EAG agrees with the company that lenvatinib is the most relevant

comparator to selpercatinib and that sorafenib is also a relevant comparator but is only used to treat <5% of patients.

Company PFS and OS naïve, unadjusted indirect treatment comparison results favoured selpercatinib over all comparators. However, these results are highly uncertain (company naïve comparisons did not adjust for any identified prognostic factors or effect modifiers, SELECT trial placebo arm data are not a good proxy for BSC OS data, the comparisons included data from any-line patients and patients with unknown *RET* fusion status [likely <4% of the comparator trial populations] and the PH assumption was not assessed for any data used in the unadjusted indirect comparisons). The EAG considers that the relative efficacy of selpercatinib versus lenvatinib, selpercatinib versus sorafenib, and selpercatinib versus BSC for systemic therapy-naïve patients with *RET*-fusion positive TC remains unknown.

Selpercatinib safety and tolerability

Based on LIBRETTO-001 trial and LIBRETTO-531 trial evidence presented in the CS, clinical advice to the EAG is that:

- selpercatinib has a reasonable safety profile and
- selpercatinib AESIs are easily managed in NHS clinical practice
- the selpercatinib safety profile appears favourable compared to cabozantinib, lenvatinib and sorafenib safety profiles.

In addition, the EAG highlights that the LIBRETTO-531 trial selpercatinib safety profile was more favourable than the physician's choice safety profile.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of selpercatinib as an option for untreated advanced *RET*-mutant MTC and patients with untreated advanced *RET* fusion-positive TC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluations for (a) *RET*-mutant MTC and (b) *RET* fusion-positive TC. The company has provided an electronic copy of the economic model which was developed in Microsoft Excel.

4.1 *Company review of published cost effectiveness evidence*

To populate the company model, the company undertook an SLR to identify HRQoL, resource use and cost data. The company also conducted a targeted literature review (TLR) to identify previous NICE technology appraisals of treatments for patients with MTC and TC.

SLR database searches were designed to retrieve articles published between 1st January 2017 and 12th August 2019. The company considered it was not necessary to update the cost effectiveness SLR as the most relevant data sources would have been identified and it was unlikely that the evidence base would have substantially increased since 2019. The company also searched conference abstracts (2017-2019) and submission documents published by Health Technology Assessment (HTA) agencies (searches performed in October 2019). Full details of the methods used by the company to identify and select relevant cost effectiveness evidence are presented in the CS (Appendix H).

The company's SLR identified 43 relevant articles and 11 potentially relevant abstracts. The company's TLR identified three technology appraisals with an additional two appraisals identified after the review was completed.[21,22,25,29,55] The company considered that the appraisals of cabozantinib for treating MTC (TA516)[21] and lenvatinib and sorafenib for treating differentiated TC after radioactive iodine (TA535)[25] are most relevant to the current appraisal. Bibliographic lists of relevant articles and systematic reviews were searched for relevant primary articles that were not identified by the electronic searches.

4.1.1 EAG critique of the company's literature review

A summary of the EAG's critique of the company's economic literature review methods is provided in Table 26.

Table 26 EAG appraisal of systematic review methods

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	No – the company did not update the original searches conducted in 2019
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	One reviewer; 10% of records were quality checked by a second independent reviewer
Was data extracted by two or more reviewers independently?	Not specified
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	No quality assessment of cost effectiveness evidence was reported
Was the quality assessment conducted by two or more reviewers independently?	n/a
Were attempts to synthesise evidence appropriate?	n/a

LRiG=Liverpool Reviews and Implementation Group; n/a=not applicable
Source: LRiG in-house checklist

4.1.2 EAG conclusion

The EAG is satisfied that the original searches of bibliographic databases, conference proceedings and other sources are broadly appropriate; however, the company did not include any updates to the original searches conducted in 2019.

4.2 *EAG summary and critique of the company's submitted economic evaluation*

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 27 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	Adequately addressed
Comparators	As listed in the scope developed by NICE	Adequately addressed
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adequately addressed
Perspective on costs	NHS and PSS	Adequately addressed
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Adequately addressed
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Adequately addressed
Synthesis of evidence on health effects	Based on systematic review	Adequately addressed
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Adequately addressed
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. The company had concerns about the LIBRETTO-001 trial HRQoL data and so used health state utility values from a vignette study (Fordham[56])
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Adequately addressed
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adequately addressed
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	Adequately addressed
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adequately addressed

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimension; HRQoL=health-related quality of life; NICE=National Institute for Health and Care Excellence; PSS=Personal Social Services; QALY=quality adjusted life year
Source: EAG assessment of NICE Reference Case[57]

Table 28 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	
Were all the important and relevant costs and consequences for each alternative identified?	No	***RET*-mutant MTC** The selected cabozantinib OS extrapolation underestimated company clinician long-term survival estimates. ***RET* fusion-positive TC** The selected selpercatinib OS distribution provided a poor statistical fit and did not provide a good visual fit to LIBRETTO-001 trial K-M data
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	Cabozantinib and lenvatinib treatment cost calculations should have used dose adherence data rather than RDI multipliers
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	Estimates of long-term survival for patients treated with selpercatinib are highly uncertain

EAG=External Assessment Group; MTC=medullary thyroid cancer; OS=overall survival; RDI=relative dose intensity; TC=thyroid cancer originating in the follicular cells
Source: Drummond and Jefferson[58] and EAG comment

4.3 *Model structure*

The company developed a de novo partitioned survival model in Microsoft Excel to evaluate the cost effectiveness of selpercatinib versus relevant comparators for untreated advanced *RET*-mutant MTC and *RET* fusion-positive TC. The company model includes three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. All patients enter the model in the PF health state. In this health state patients are at risk of moving to the PD or death health states. Patients in the PD health state are only at risk of moving to the death health state. Death is an absorbing health state (patients cannot transition to another health state from death). An illustration of the company model structure is presented in Figure 1.

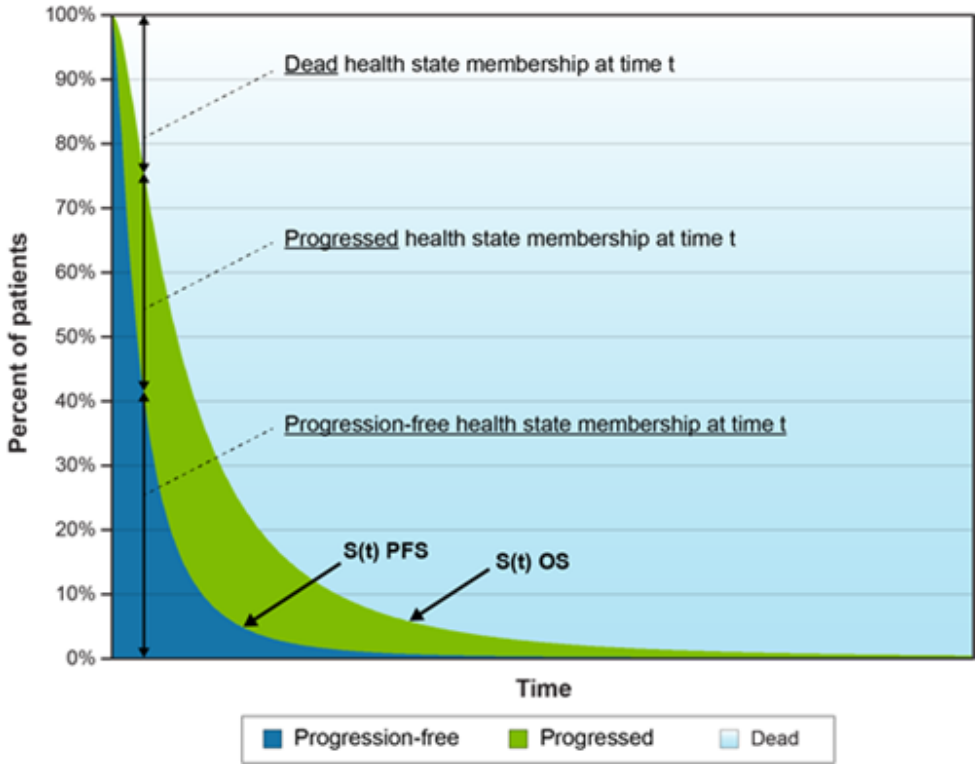

Figure 1 Company model structure

PFS=progression-free survival; OS=overall survival
Source: CS, Figure 35

4.4 *Population*

4.4.1 *RET*-mutant MTC

The company defined the population of interest as patients aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy and who have not previously received systemic therapy. The company model is populated with LIBRETTO-001 trial[31] data; specifically, the any-line MTC population (n=295) which comprises patients who are cabozantinib/vandetanib-naïve (n=143) and those who have had previously received cabozantinib or vandetanib (n=152). The company considered that the LIBRETTO-001 trial any-line population aligned with the available data from the EXAM trial[45] of cabozantinib (the intention-to-treat [ITT] population included patients who were systemic therapy-naïve and systemic therapy-experienced) and provided a larger dataset than the cabozantinib/vandetanib-naïve population. Baseline age and sex data for the *RET*-mutant MTC population included in the company model are presented in Table 29.

4.4.2 *RET* fusion-positive TC

The company defined the population of interest as patients aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy and who have not previously received systemic therapy. The company model is populated with LIBRETTO-001 trial[31] data;

specifically, the any-line *RET* fusion-positive TC population (n=65) which comprises systemic therapy-naïve (n=24) and systemic therapy-experienced patients (n=41). The company considered the any-line population data aligned with SELECT trial[37] data (lenvatinib) and this dataset was larger than the systemic therapy-naïve population dataset. *RET* fusion-positive TC baseline age and sex data were used in the model (Table 29).

Table 29 Company model baseline age and sex data

Population	Mean age (SD)	Sex (% female)
RET-mutant MTC	[redacted]	39.0
RET fusion-positive TC	[redacted]	50.8

CS=company submission; MTC=medullary thyroid cancer; *RET*=rearranged during transfection; SD=standard deviation; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 59

4.5 *Interventions and comparators*

The intervention of interest for both economic analyses is selpercatinib (160mg) administered orally twice daily in 28-day cycles until treatment discontinuation due to progressive disease, unacceptable toxicity or other reasons.

4.5.1 *RET*-mutant MTC

The company included cabozantinib and BSC in the economic model as comparators to align with standard care in UK clinical practice. Clinical experts consulted by the company indicated that cabozantinib is used in clinical practice by 80% to 90% of patients, with the remainder (adolescents or patients otherwise ineligible or unsuitable to receive cabozantinib) receiving BSC. The dosing schedule for cabozantinib in the company model is 140mg orally once daily until progressive disease or unacceptable toxicity; this is in line with information provided in the SmPC[59] and the EXAM trial.[45] The company considered that EXAM trial[45] placebo arm data were a suitable proxy for BSC data; in the model, BSC was assumed to consist of routine care and monitoring (costs described in Section 4.9.2).

4.5.2 *RET* fusion-positive TC

Lenvatinib and BSC were included in the company model as comparators as they aligned with standard care in UK clinical practice. Clinical experts consulted by the company indicated that lenvatinib was used by 90% to 95% of patients who receive MKIs and the remainder of patients who receive an MKI are prescribed sorafenib. The company therefore considered that sorafenib was not a relevant comparator for the advanced *RET* fusion-positive TC population. Company clinical experts estimated that BSC would be received by approximately 10% of patients.

In the company model, the lenvatinib dosing schedule was 24mg orally once daily until progressive disease or unacceptable toxicity; this is in line with the SELECT trial[37] dosing schedule. The company considered that the SELECT trial placebo arm data were a suitable proxy for BSC data; in the model, BSC was assumed to consist of routine care and monitoring.

4.6 *Perspective, time horizon and discounting*

In the original company base case, a time frame of 25 years was used to represent a lifetime horizon and the cycle length was one week. In response to Clarification Question B4, the company adopted a time horizon of 35 years for their revised base case. In line with the NICE Reference Case,[57] a discount rate of 3.5% per annum was applied to costs and outcomes and the analysis was conducted from a NHS and Personal Social Services perspective. Costs based on previous cost-years or in other currencies were inflated to the model cost-year (2023) using the Consumer Prices Health Index[60] and/or converted to UK £, as applicable.

4.7 *Treatment effectiveness and extrapolation*

4.7.1 *RET*-mutant MTC

Overall survival

The company conducted unanchored MAICs to estimate the comparative effectiveness of selpercatinib versus cabozantinib and selpercatinib versus BSC, using any-line LIBRETTO-001 trial *RET*-mutant MTC data and EXAM trial[46,45] data. LIBRETTO-001 trial patient characteristics were matched to EXAM trial[36] cabozantinib arm *RET*-mutant subgroup patient characteristics to calculate weights which were then applied to the LIBRETTO-001 trial OS K-M data (Table 30).

EXAM trial *RET* mutant MTC OS K-M data were not reported; therefore, EXAM trial *RET* M918T-positive placebo OS K-M data were digitised (Guyot[61] algorithm). This approach was supported by clinical expert advice provided during TA742[29] who considered that *RET* M918T-positive subgroup placebo arm outcomes may be similar to overall *RET*-mutant population outcomes. The company considered that this assumption was not supported for patients treated with cabozantinib as there was evidence to suggest that cabozantinib was more effective in the M918T-positive subgroup than in the overall *RET*-mutant population.[46] Therefore, the company estimated OS for patients treated with cabozantinib by applying the EXAM trial HR (cabozantinib versus placebo, *RET*-mutant) to the selected BSC distribution.

The company fitted standard (e.g., exponential, Weibull) and flexible (i.e., spline) parametric distributions to generate survival estimates over the model time horizon; the approach used was in line with NICE Decision Support Unit (DSU) TSD 14[62] advice. The company fitted

unstratified and stratified models, the latter allow model parameters to vary by treatment; this means that goodness of fit statistics for all models can be compared across treatment arms. Company model selection involved consideration of statistical fit, visual inspection of the observed OS K-M curves, the clinical plausibility of extrapolations (based on clinical expert estimates of long-term survival) and NICE Committee preferences during TA742[29] (based on an earlier data cut of the same analysis sets of the LIBRETTO-001 trial).

The company considered that the stratified Weibull model provided the most clinically plausible estimates of long-term survival for patients treated with selpercatinib and BSC, and aligned with NICE Committee preferences in TA742[29]; therefore, this distribution was used in the company base case. The company considered that the stratified Weibull model allowed cabozantinib to be modelled via a HR (i.e., proportional hazards could be assumed).

Table 30 Company base case approaches to generating OS estimates: *RET*-mutant MTC population

Treatment	Data source	Method
Selpercatinib	Propensity score weighted LIBRETTO-001 trial OS K-M data for *RET*-mutant population (any line)	Stratified Weibull distribution
Cabozantinib	Selected BSC extrapolation	Apply HR reported by Schlumberger[46]
BSC	Unweighted EXAM trial placebo arm OS K-M data for *RET* M918T-positive population	Stratified Weibull distribution

BSC=best supportive care; CS=company submission; HR=hazard ratio; K-M=Kaplan-Meier; MTC=medullary thyroid cancer; OS=overall survival; *RET*=rearranged during transfection
Source: CS, Table 57 and Table 77

All distributions used to generate OS estimates were capped by age- and sex-matched general population mortality rates sourced from the Office for National Statistics (ONS) national life tables.[63]

Progression-free survival

For patients treated with selpercatinib and BSC, PFS was modelled using the same data sources as for OS (Table 31). PFS K-M curves were available from the EXAM trial[45] for patients with *RET*-mutant MTC who were treated with cabozantinib; these curves were digitised to create pseudo cabozantinib PFS K-M data.

The company followed the same model fitting and selection process as undertaken for OS. The company considered that the (unstratified) loglogistic distribution provided the most accurate long-term PFS estimates for patients treated with selpercatinib, cabozantinib and BSC when compared to clinician estimates, and aligned with NICE Committee preferences in TA742[29]; therefore, this distribution was used in the company base case analysis.

Table 31 Company base case approaches to generating PFS estimates: *RET*-mutant MTC population

Treatment	Data source	Method
Selpercatinib	Propensity score weighted LIBRETTO-001 trial PFS K-M data for *RET*-mutant population (any-line population)	Loglogistic distribution
Cabozantinib	Unweighted cabozantinib EXAM trial PFS K-M data for *RET*-mutant population	
BSC	Unweighted placebo EXAM trial PFS K-M data for *RET*-mutant population	

BSC=best supportive; CS=company submission; K-M=Kaplan-Meier; MTC=medullary thyroid cancer; PFS=progression-free survival; *RET*=rearranged during transfection
Source: CS, Table 57 and Table 77

The company implemented constraints in the model to ensure that outcomes remained logically consistent (i.e., PFS≤OS).

4.7.2 *RET* fusion-positive TC

Overall survival

The company conducted a naïve, unadjusted indirect treatment comparison to estimate the comparative effectiveness of selpercatinib versus lenvatinib and versus BSC. The company considered that there was an insufficient number of patients and lack of comparability between the LIBRETTO-001 trial and comparator trials for an adjusted indirect comparison to be feasible. Table 32 outlines the data sources used by the company to estimate OS for patients treated with selpercatinib, lenvatinib and BSC.

Table 32 Company base case approaches to generating OS estimates: *RET* fusion-positive TC population

Treatment	Data source	Method
Selpercatinib	LIBRETTO-001 trial, selpercatinib arm (*RET* fusion-positive TC, any-line), OS K-M data	Piecewise exponential distribution
Lenvatinib	SELECT trial, lenvatinib arm (any-line), RPSFT-adjusted OS K-M	
BSC	SELECT trial, placebo arm (any-line), RPSFT-adjusted OS K-M data	

BSC=best supportive; CS=company submission; K-M=Kaplan-Meier; OS=overall survival; *RET*=rearranged during transfection; RPSFT=rank-preserving structural failure time
Source: CS, Table 58 and Table 78

The company followed the same model fitting and selection processes used when fitting distributions to *RET*-mutant MTC OS data. The company considered that the piecewise exponential distribution provided the most accurate long-term OS estimates for patients treated with selpercatinib, lenvatinib and BSC when compared to clinician estimates; this distribution was used in the company base case analysis.

Progression-free survival

For patients treated with selpercatinib, lenvatinib and BSC, PFS was modelled using the same data sources as for OS (Table 33). The company considered that, for selpercatinib, lenvatinib and BSC, the stratified Weibull distribution provided the most accurate long-term PFS

estimates when compared to clinician estimates, and aligned with NICE Committee preferences in TA742[29]; this distribution was used in the company base case analysis.

Table 33 Company base case PFS approaches: *RET* fusion-positive TC population

Treatment	Data source	Method
Selpercatinib	LIBRETTO-001 trial PFS K-M data for *RET* fusion-positive TC population (any-line)	Stratified Weibull distribution
Lenvatinib	SELECT trial[37] RPSFT-adjusted OS K-M data for patients receiving lenvatinib (any-line)	
BSC	SELECT trial[37] RPSFT-adjusted OS K-M data for patients receiving placebo (any-line)	

BSC=best supportive care; CS=company submission; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; RPSFT=rank-preserving structural failure time; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS Table 58 and Table 78

4.8 *Health-related quality of life*

4.8.1 Health state utility values

The company considered that EORTC QLQ-C30 data from the LIBRETTO-001 trial produced implausible health state utility values when mapped to EQ-5D data (CS, Table 81). Therefore, the company used health state utility values sourced from a vignette study[56] that had elicited utility values for (radioactive iodine refractory) differentiated TC from a sample (n=100) of the UK general population (Table 34). The company used the health state utility values in Table 34 to estimate the HRQoL of patients with *RET*-mutant MTC and patients with *RET* fusion-positive TC. In the company model, health state utility values were adjusted to account for the decrease in HRQoL with age, using a multiplicative approach derived from Ara & Brazier.[64]

Table 34 Company base case health state utility values

Health state	Mean (SD)
Progression-free	0.80 (0.018)
Progressed	0.50 (0.028)

CS=company submission; SD=standard deviation
Source: CS, Table 84

The company modelled HRQoL reductions for patients experiencing Grade≥3 AEs; AEs with at least a 2%-point difference in incidence between treatments were included in the model. Most AEs were assumed to be associated with the same utility decrement and all were assumed to have equal duration (Table 35); this approach is consistent with the approach used in TA535[25] and in TA516.[21] Utility decrements were multiplied by duration (days) to estimate QALY losses due to AEs which were assumed to occur in the first model cycle.

Table 35 Adverse event utility decrements and durations: patients with advanced *RET*-mutant MTC and *RET* fusion-positive TC

Adverse event	Utility decrement		Duration (days)
	RET-mutant MTC population	*RET* fusion-positive population	
Diarrhoea	−0.110	−0.380	30.4
Hand foot syndrome	−0.110	−0.280	30.4
Hypertension	−0.110	−0.110	30.4
ECG QT prolonged	−0.110	−0.110	30.4
Decreased weight	−0.110	−0.110	30.4
Abdominal pain	−0.110	n/a	30.4
Haemorrhage	−0.110	n/a	30.4
Dysphagia	−0.110	n/a	30.4
Fatigue	−0.110	−0.080	30.4
Decreased appetite	−0.110	−0.110	30.4
Rash	−0.110	−0.110	30.4
Asthenia	−0.110	−0.110	30.4
Mucosal inflammation	−0.110	−0.110	30.4
Vomiting	−0.110	−0.110	30.4
Dyspnoea	−0.110	−0.110	30.4
Headache	−0.110	−0.110	30.4
Back pain	−0.110	−0.110	30.4
Alanine aminotransferase increased	−0.110	−0.110	30.4
Aspartate aminotransferase increased	−0.110	−0.110	30.4
Hyponatraemia	−0.110	n/a	30.4
Thrombocytopenia	n/a	-0.110	30.4
Lymphopenia	−0.110	−0.110	30.4
Pneumonia	−0.110	−0.110	30.4
Hypocalcaemia	−0.110	−0.110	30.4
Leukopenia	n/a	−0.110	30.4
Nausea	n/a	−0.110	30.4
Stomatitis	n/a	−0.110	30.4
Proteinuria	n/a	−0.110	30.4
Neutropenia	n/a	−0.110	30.4
Confused state	n/a	−0.110	30.4
Dehydration	−0.110	−0.110	30.4
Weight increased	−0.110	−0.110	30.4
Ascites	−0.110	−0.110	30.4
Sepsis	−0.110	−0.110	30.4
Hyperkalaemia	−0.110	−0.110	30.4
Hypophosphatemia	−0.110	−0.110	30.4
Hyperglycaemia	−0.110	−0.110	30.4
Hypercalcemia	−0.110	−0.110	30.4

CS=company submission; ECG QT=electrocardiogram; MTC=medullary thyroid cancer; n/a=not applicable; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 82 and Table 83

4.9 *Resources and costs*

4.9.1 Drug costs

Drug unit costs and the modelled dosing schedules for selpercatinib, cabozantinib and lenvatinib are presented in Table 36. All treatments are available to the NHS at confidential discounted PAS prices.

Table 36 Drug acquisition costs

Treatment	Dosing schedule	Capsule strength	Capsules per pack	Cost per pack
Selpercatinib	160mg orally twice daily	80mg	112	£8,736
		40mg	168	£6,552
Cabozantinib	140mg orally once daily	80mg	112	£4,800
		20mg	112	£4,800
Lenvatinib	24mg orally once daily	4mg	30	£1,437
		10mg	30	

Source: CS, Table 85

Dose adjustments

In the company model, dose adjustments were made to account for treatment toxicity. The company assumed that no dose reductions would occur during the first four model cycles but did assume that some patients would receive an adjusted selpercatinib dose (<160mg) at the start of the model as observed in the LIBRETTO-001 trial (Table 37). In subsequent model cycles, a proportion of patients were assumed to receive a selpercatinib dose within the 20-120mg range such that the mean dose intensity matched that observed in the LIBRETTO-001 trial ([redacted]% for *RET*-mutant MTC; [redacted]% for *RET* fusion-positive TC).

Table 37 Selpercatinib dose adjustments in economic model

Treatment cycle	Dose (mg)	Proportion of patients on dose (%)	
		RET-mutant MTC population	*RET* fusion-positive TC population
1	160	[redacted]	[redacted]
	120	[redacted]	[redacted]
	80	[redacted]	[redacted]
2	160	[redacted]	[redacted]
	120	[redacted]	[redacted]
	80	[redacted]	[redacted]
	60	[redacted]	[redacted]
	40	[redacted]	[redacted]
	20	[redacted]	[redacted]

CS=company submission; MTC=medullary thyroid cancer; n/a=not applicable; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 87

For cabozantinib and lenvatinib, after Week 4, a mean relative dose intensity (RDI) multiplier was applied to all treatment doses administered. The company considered that there were no cabozantinib RDI data available and therefore assumed that the RDI value used in the company *RET*-mutant MTC model was equivalent to LIBRETTO-001 trial mean selpercatinib RDI (■). The lenvatinib mean RDI multiplier reported in TA535[25] (71.67%) was used in the company *RET* fusion-positive TC model.

Time on treatment

For cabozantinib and lenvatinib, the company assumed that time on treatment was equal to PFS. For patients treated with selpercatinib, the company modelled a delay in treatment discontinuation equal to the mean time on post-progression treatment observed in the LIBRETTO-001 trial systemic therapy-naïve populations (*RET*-mutant MTC: ▌ weeks; *RET* fusion-positive TC: ▌ weeks). Clinical advice to the company[23] was that no subsequent treatments are routinely available for NHS for patients who discontinue treatment; therefore, in the model patients did not receive any subsequent treatment after treatment discontinuation.

4.9.2 Healthcare resource use

Best supportive care (health state) costs

The company considered that BSC comprised routine care and monitoring (i.e., no active intervention) and assumed that resource use in the progression-free health state was equivalent to resource use in the progressed disease health state (as recommended by the EAG in TA742[29]). The health state resource use and unit costs applied in the model are presented in Table 38 (sourced from TA516[21] and NHS Cost Collection[65]).

Table 38 Company model unit costs and health state resource use for patients with advanced *RET*-mutant MTC and *RET* fusion-positive TC

Resource	Model health state		Unit cost	Source
	Progression-free	Progressed disease		
Consultant-led outpatient visits (range)	12 (4 to 16)	6 (4 to 12)	£162.93	NHS Cost Collection[65] (2021/22) consultant-led, non-admitted face-to-face attendance, follow-up WF01A
Nurse-led outpatient visits (range)	4 (0 to 6)	6 (0 to 6)	£130.74	NHS Cost Collection[65] (2021/22) non-consultant-led, non-admitted face-to-face attendance, follow-up WF01A
Blood tests	12	6	£4.70	NHS Cost Collection[65] (2021/22) directly accessed pathology, phlebotomy DAPS08
CT scan	4	4	£99.88	NHS Cost Collection[65] (2021/22) outpatient, computerised tomography scan of more than 3 areas RD27Z

CS=company submission; CT=computerised tomography; MTC=medullary thyroid cancer; NHS=National Health Service; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 88

The company model also included palliative care costs (Table 39); these were sourced from Unit Costs of Health and Care[66] and NHS Cost Collection[65] and were applied when patients transitioned to the death health state.

Table 39 Company model palliative care costs for patients with advanced *RET*-mutant MTC and *RET* fusion-positive TC

Resource	Cost	Source
Palliative care	£10,676.25	NICE TA516,[21] PSSRU (2022)[66]
Palliative chemotherapy	£1,016.14	NHS Cost Collection (2021/2022),[65] other, procure chemotherapy drugs for regimens in band 1-10, SB01Z-SB10Z

CS=company submission; MTC=medullary thyroid cancer; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 89

Administration and monitoring costs

The company included the NHS Cost Collection[65] cost (every 30 days) for the administration of oral drugs (12 minutes of pharmacy time [£11.40]); this is in line with the approach taken in TA742.[29] The company model included the cost of seven electrocardiograms (ECGs) as part of the cost of monitoring treatment with selpercatinib; this is in line with the requirements outlined in the selpercatinib SmPC.[27] The cost of a single ECG (£159.36) was sourced from NHS Cost Collection.[65]

Diagnostic testing

The company base case analysis included the cost of *RET* testing; this is in line with the preference of the TA911[34] NICE Appraisal Committee. The proportion of patients testing positive in each population and the unit cost of a test are presented in Table 40. The proportion of patients with advanced *RET*-mutant MTC testing positive was calculated using data from

published studies (Taccaliti[67] and Wells[68]). The screen-positivity rate for patients with advanced *RET*-fusion TC was sourced from Liu.[69]

Table 40 Company diagnostic testing cost parameters

Parameter	*RET*-mutant MTC	*RET* fusion-positive TC
Screen-positive rate	61.2%	6.8%
RET test cost	£34	

CS=company submission; MTC=medullary thyroid cancer; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 92

4.9.3 Adverse event management costs

AE management unit costs are presented in Table 41; these were sourced from NHS Cost Collection[65] (see CS, Table 91 for NHS Cost Collection codes) or based on assumption.

Table 41 Adverse event management costs for advanced *RET*-mutant MTC and *RET* fusion-positive TC

Adverse event	Mean cost per episode
Diarrhoea	£3,407.28
Hand foot syndrome	£1,646.87
Hypertension	£2,300.49
ECG QT prolonged	£1,649.11
Decreased weight	£3,042.95
Abdominal pain	£1,789.01
Haemorrhage	£500.00 (assumption)
Dysphagia	£1,367.91
Fatigue	£0.00 (assumption)
Decreased appetite	£3,042.95
Rash	£1,646.87
Asthenia	£0.00 (assumption)
Mucosal inflammation	£1,949.19
Vomiting	£3,042.95
Dyspnoea	£1,446.19
Headache	£0.00 (assumption)
Back pain	£2,096.09
Alanine aminotransferase increased	£0.00 (assumption)
Aspartate aminotransferase increased	£0.00 (assumption)
Hyponatraemia	£1,708.97
Thrombocytopenia	£0.00 (assumption)
Lymphopenia	£4,776.75
Pneumonia	£2,067.76
Hypocalcaemia	£1,708.97
Leukopenia	£0.00 (assumption)
Nausea	£0.00 (assumption)
Stomatitis	£0.00 (assumption)
Proteinuria	£0.00 (assumption)
Neutropenia	£0.00 (assumption)
Confused state	£0.00 (assumption)
Dehydration	£500.0 (assumption)
Weight increased	£0.00 (assumption)
Ascites	£1,789.01
Sepsis	£5,779.96
Hyperkalaemia	£0.00 (assumption)
Hypophosphatemia	£0.00 (assumption)
Hyperglycaemia and hypercalcemia	£0.00 (assumption)

CS=company submission; ECG QT=electrocardiogram; MTC=medullary thyroid cancer; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 90 and Table 91

4.10 *Severity modifier*

The company used the severity modifier tool developed by the School for Health and Related Research at the University of Sheffield[70] to calculate the absolute and proportional QALY shortfalls for each analysis. The company used the baseline population characteristics presented in Table 29 to calculate expected general population QALYs. The results of the QALY shortfall analyses are presented in Table 42. The company considered that, for the *RET*-mutant MTC population, selpercatinib was eligible for a 1.2x severity modifier when compared to cabozantinib and when compared to BSC. The company considered that, for the *RET* fusion-positive TC population, selpercatinib was not eligible for a severity modifier when compared to lenvatinib but was eligible for a severity modifier (x1.2) when compared to BSC.

Table 42 Results from the company QALY shortfall analyses

Population	Total QALYs for patients receiving current standard of care	Expected general population QALYs	Absolute QALY shortfall	Proportional QALY shortfall	Severity modifier
RET-mutant MTC	Cabozantinib: 2.11	14.34	12.23	85.29%	1.2
	BSC: 1.51		12.83	89.47%	1.2
RET fusion-positive TC	Lenvatinib: 2.62	13.38	10.76	80.42%	1
	BSC: 1.27		12.11	90.51%	1.2

BSC=best supportive; CS=company submission; MTC=medullary thyroid cancer; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: CS, Table 94

5 COST EFFECTIVENESS RESULTS

The company provided updated cost effectiveness results in response to the EAG's clarification questions.

5.1 *RET-mutant MTC*

The company presented pairwise comparison results as BSC is only received by patients who are ineligible for cabozantinib (comparators would typically be received by the same patient population). Deterministic and probabilistic results are presented in Table 43 and Table 44 respectively with the confidential PAS discount for selpercatinib applied. The company considered selpercatinib is eligible for a 1.2x severity modifier versus both cabozantinib and BSC, therefore the EAG has presented results with the severity modifier applied.

Table 43 Company clarification base case deterministic pairwise results: *RET*-mutant MTC population (PAS price for selpercatinib)

Treatment	Total costs	QALYs	Incremental costs	Incremental QALYs with x1.2x severity modifier	ICER (£/QALY) with x1.2x severity modifier
Selpercatinib	[redacted]	[redacted]	-	-	-
Cabozantinib	£89,900	2.080	[redacted]	[redacted]	£29,713
BSC	£17,089	1.508	[redacted]	[redacted]	£39,481

BSC=best supportive care; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALY=quality adjusted life year; *RET*=rearranged during transfection
Source: Company clarification model

Table 44 Company clarification base case probabilistic pairwise results: *RET*-mutant MTC population (PAS price for selpercatinib)

Treatment	Total costs	QALYs	Incremental costs	Incremental QALYs with 1.2x severity modifier	ICER (£/QALY) with 1.2x severity modifier
Selpercatinib	[redacted]	[redacted]	-	-	-
Cabozantinib	£89,785	2.107	[redacted]	[redacted]	£29,877
BSC	£17,110	1.516	[redacted]	[redacted]	£39,458

BSC=best supportive care; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALY=quality adjusted life year; *RET*=rearranged during transfection
Source: Company clarification model

5.2 *RET fusion-positive TC*

Deterministic and probabilistic results for the *RET* fusion-positive TC population are presented in Table 45 and Table 46 respectively with the confidential PAS discount for selpercatinib applied. The company considered selpercatinib is eligible for a 1.2x severity modifier versus BSC therefore the EAG has presented results with the severity modifier applied for this pairwise comparison.

Table 45 Company clarification base case deterministic pairwise results: *RET* fusion-positive TC population (selpercatinib PAS price)

Treatment	Total costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	-	-	-
Lenvatinib	£96,507	2.622	[redacted]	[redacted]	£36,329
BSC	£16,030	1.272	[redacted]	[redacted]*	£37,050*

* Severity modifier (x1.2) applied for selpercatinib versus BSC only
BSC=best supportive care; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Company clarification model

Table 46 Company clarification base case probabilistic pairwise results: *RET* fusion-positive TC population (selpercatinib PAS price)

Treatment	Total costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	-	-	-
Lenvatinib	£96,510	2.631	[redacted]	[redacted]	£36,347
BSC	£15,983	1.277	[redacted]	[redacted]*	£37,025*

* Severity modifier (x1.2) applied for comparison of selpercatinib versus BSC only
BSC=best supportive care; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Company clarification model

5.3 *Sensitivity analyses*

The company varied parameter input values individually in deterministic sensitivity analyses (DSA). Upper and lower values were based on confidence intervals or an assumed standard error of 10% of the mean base case value. For the *RET*-mutant MTC population, the key drivers of cost effectiveness were the discount rate used for outcomes and costs, the progression-free health state utility value and costs and the hazard ratio applied for cabozantinib OS. For the *RET* fusion-positive TC population, the key drivers of cost effectiveness were the discount rate for outcomes and costs, the progression-free health state utility value and costs.

5.4 *Scenario analyses*

The company conducted scenario analyses exploring alternative OS and PFS extrapolations and assuming drug wastage. For the *RET*-mutant MTC population, cost effectiveness results were most sensitive when assuming drug wastage and using the spline 1 knot as the selected PFS distribution (for all treatment arms). For the *RET* fusion-positive TC population, cost effectiveness results were most sensitive when using the spline 1 knot as the selected PFS distribution (for all treatment arms).

5.5 *Validation*

The company's cost effectiveness model was based on the model submitted in TA742.[29] The company's original model was reviewed by a health economist and UK clinical thyroid cancer experts. The company considered that full validation of the updated model used in this

submission was not necessary but updated clinical data and other key model aspects were discussed and validated with UK clinical experts.[23] Verification of input data and validation of model code were performed by an independent reviewer and an independent health economist.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company submitted an updated economic model in response to clarification, developed in Microsoft® Excel, to generate cost effectiveness results for the *RET*-mutant MTC and *RET* fusion-positive TC populations. The EAG is satisfied that the company model algorithms are accurate and that parameter values in the model match the values presented in the CS. A summary of the EAG's critique is presented in Table 47. Where model parameters differ by population, the EAG has provided a critique in separate sub-sections.

Table 47 Summary of EAG critique of company cost effectiveness model: *RET*-mutant MTC and *RET* fusion-positive TC populations

Aspect considered	EAG comment	Section of EAG report
Model structure	• The company model structure is appropriate	n/a
Population	• Use of any-line LIBRETTO-001 trial data and limitations of the company unanchored MAIC may not generate accurate treatment effect estimates of selpercatinib versus the relevant comparators for a cabozantinib/vandetanib-naïve *RET*-mutant MTC population but are unlikely to change the conclusion that selpercatinib improves PFS and OS versus cabozantinib and BSC • The company indirect treatment comparison of LIBRETTO-001 and SELECT[37] trial population data is a naïve, unadjusted comparison of data of any-line patients with and without *RET* mutations. Therefore, the efficacy of selpercatinib versus comparators for the *RET* fusion-positive TC population is uncertain	6.1
Comparators	• The comparators included in the economic model represent NHS standard of care. Clinical advice to the EAG agreed with the company that sorafenib is used in a minority (<5%) of patients with *RET* fusion-positive TC, therefore exclusion of sorafenib from the economic model is reasonable • Clinical advice to the EAG is that EXAM[45] trial and SELECT[25] trial placebo arm data provide reasonable proxies of the experience of patients receiving BSC (who would otherwise receive active treatment) in the *RET*-mutant MTC and *RET* fusion-positive TC populations respectively	n/a
Overall survival	• Company model long-term OS estimates for patients with *RET*-mutant MTC and *RET* fusion-positive TC treated with selpercatinib are based on expert opinion; these values imply a substantial post-progression survival relative to comparators and are uncertain • Company cabozantinib 10-year and 20-year OS estimates are below the expected values suggested by company clinical experts; the EAG considers that the stratified spline 1 knot distribution provides more clinically plausible estimates than the stratified Weibull distribution used in the company base case (*RET*-mutant MTC population) • The company generated BSC OS estimates using the stratified Weibull distribution which approximates the EXAM trial[46] placebo arm OS K-M data and generates OS estimates that are within the range suggested by the company clinical experts (*RET*-mutant MTC population) • The company used a piecewise exponential distribution to approximate SELECT trial[25] lenvatinib and placebo arm OS K-M data. This distribution generates OS estimates that are within the ranges suggested by the company clinical experts	6.2

Aspect considered	EAG comment	Section of EAG report
Progression-free survival	• For the *RET*-mutant MTC population, the unstratified loglogistic distribution approximates the LIBRETTO-001 trial and EXAM trial[45] PFS K-M data for each treatment reasonably well and provides clinically plausible long-term PFS estimates for selpercatinib, cabozantinib and BSC. An unstratified model may not be appropriate as there is evidence of non-proportional hazards for selpercatinib versus cabozantinib; however, all fitted stratified models generate clinically implausible PFS estimates • For the *RET* fusion-positive TC population, the stratified Weibull distribution approximates the LIBRETTO-001 trial and SELECT trial[37] PFS K-M data for each treatment reasonably well and provides clinically plausible long-term PFS estimates for selpercatinib, lenvatinib and BSC	6.3
Model time horizon	• In response to Clarification Question B4, the company increased the model time horizon to 35 years so that, at the end of the model time horizon, <2% of patients in each arm are alive	n/a
Drug costs	• The company applied RDI multipliers to doses of cabozantinib and lenvatinib. As the lenvatinib and cabozantinib pack prices are the same regardless of dose size, dose adherence data should have been used to calculate treatment costs instead of RDI. When discussing cabozantinib, the NICE TA928[1] AC preferred adherence data to RDI data • Cabozantinib adherence data may be available from the LIBRETTO-531 trial[32]	6.4
Utility values	• The progressed disease health state utility value is implausibly low as the company model predicts patients with *RET*-mutant MTC or *RET* fusion-positive TC will survive for several years after progression. The EAG considers that the any-line *RET* fusion-positive TC population health state utility values generated by mapping LIBRETTO-001 trial EORTC-QLQ-C30 to EQ-5D-3L data are more plausible than the utility values chosen by the company and align with the NICE Reference Case[57]	6.5
Health care resource use	• Clinical advice to the EAG is that health care resource use estimates are reasonable	n/a
AE	• The assumption of an equivalent utility decrement for all AEs may not be accurate. However, changing this assumption has minimal impact on cost effectiveness results	n/a
PSA	• For selpercatinib OS, the company adjustment factor is not varied in the company PSA; this could result in implausible long-term OS estimates. Therefore, the EAG has excluded selpercatinib OS from the *RET*-mutant MTC and *RET* fusion-positive TC population PSA • Varying the EAG preferred stratified spline 1 knot distribution (cabozantinib OS) in the PSA generates implausible cabozantinib QALY values. The EAG has therefore excluded cabozantinib OS from the PSA • RET-mutant MTC population BSC OS data were varied in the PSA • To generate OS results for the *RET* fusion-positive TC population, the company model only allows a jointly fitted distribution for all treatments (same shape parameter, different scale parameters). When excluding selpercatinib OS from the PSA, lenvatinib and BSC OS are also excluded	6.2.1

AC=Appraisal Committee; AE=adverse event; BSC=best supportive care; EAG=External Assessment Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; K-M=Kaplan-Meier; MTC=medullary thyroid cancer; n/a=not applicable; OS=overall survival; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; RDI=relative dose intensity; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

6.1 *Populations*

6.1.1 *RET*-mutant MTC population

The company conducted unanchored MAICs using LIBRETTO-001 trial and EXAM trial[46] any-line population data; differences in baseline population characteristics were adjusted for,

including whether patients had previously been treated with a TKI/MKI. The company used any-line population data as EXAM trial[46] outcome data were not reported by line of treatment. The LIBRETTO-001 and EXAM trial[46] populations may not be comparable due to differences in prior therapies ([redacted]% of LIBRETTO-001 trial any-line patients had received vandetanib as a prior systemic therapy, compared to 10.3% of EXAM trial[36] patients). The extent to which differences in prior systemic therapies impact the comparability of results is not known. Clinical advice to the EAG is that, compared to cabozantinib/vandetanib-naïve population data, any-line LIBRETTO-001 trial population data may underestimate the efficacy of selpercatinib.

LIBRETTO-531 trial[32] clinical effectiveness results are likely to be the most relevant for patients with *RET*-mutant MTC in this appraisal; however, the EAG considers the data are currently of limited value for informing the economic model as follow-up is short (median interim PFS follow up in the selpercatinib arm of [redacted] months compared to [redacted] months in the LIBRETTO-001 trial).

6.1.2 *RET* fusion-positive TC population

The EAG agrees with the company that carrying out an adjusted indirect comparison is not feasible due to the small size of the LIBRETTO-001 trial *RET* fusion-positive TC population. However, the EAG considers that a naïve, unadjusted indirect comparison cannot provide a robust estimate of the relative efficacy of selpercatinib versus comparators for the *RET* fusion-positive TC population; differences in patient populations and trial design may affect results.

6.2 *Overall survival*

6.2.1 *RET*-mutant MTC population

The company fitted 19 parametric distributions to:

- the selpercatinib OS MAIC weighted curve (effective sample size=157)
- EXAM trial[46] *RET* M918T placebo arm OS data (n=45)

The company generated Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics by jointly fitting (unstratified and stratified) parametric distributions to combined selpercatinib, cabozantinib and BSC OS data. This approach allowed AIC and BIC statistics to be compared between treatment arms. Stratifying by treatment relaxed the PH assumption implied by unstratified models. The company concluded that the AIC and BIC statistics showed that the goodness of fit to the observed data was similar for all distributions (CS, p162). Identifying the most appropriate distributions was difficult, therefore, the company asked UK clinical experts to provide estimates, at different landmark timepoints, of the proportions of patients anticipated to be alive following each treatment. The company clinical experts provided three landmark survival estimates: the most likely value, the lower plausible limit and

the upper plausible limit. The lower and upper plausible limits were defined as being extremely unlikely that the true value is less than/higher than this value.

Whilst the company has chosen to generate OS estimates using the same distribution for all three treatments, the EAG considers that there is sufficient justification to use different distributions to generate OS estimates as selpercatinib has a different mechanism of action to cabozantinib (and to BSC). The different mechanisms of action of selpercatinib and cabozantinib also means that the goodness of fit statistics for jointly fitted models estimated by the company are of limited value for model selection.

Selpercatinib

The company chose to use a stratified Weibull distribution to generate OS estimates for patients treated with selpercatinib; the company considered that the Weibull distribution generated estimates that most closely aligned with UK clinical expert estimates. However, in the original company base case, the OS estimates generated by this distribution were substantially higher than company clinical expert estimates.[23] In response to Clarification Question B1, the company applied an adjustment factor at 5 years to the stratified Weibull distribution; the adjusted distribution 10-year and 20-year survival estimates aligned more closely with company clinical expert estimates than the (original) unadjusted distribution estimates. The application of the adjustment factor resulted in a kink in the selpercatinib OS curve at 5 years (i.e., a step change in the mortality hazard). Although such a step change is clinically implausible, the EAG considers the long-term OS estimates generated by the adjusted distribution are more clinically plausible than the estimates generated by the original unadjusted distribution.

Although the parameterisation of the selpercatinib OS distribution was varied in the PSA, the adjustment factor (and the time applied) was not varied. The EAG considers that it is inappropriate to vary only the parameterisation as, when using a fixed adjustment factor applied at a fixed time point, individual PSA runs may produce long term OS estimates that do not align with company clinical advice. The EAG has therefore excluded selpercatinib OS from the PSA.

The EAG has generated cost effectiveness results using different adjustment factors at 5 years; these generate 10-year and 20-year survival estimates that are in line with the upper and lower bounds of the survival estimates suggested by company clinical experts (Table 48).

Table 48 Selpercatinib OS estimates: *RET*-mutant MTC population

Distribution	10-year survival	20-year survival
Clinical experts' most likely value	[redacted]	[redacted]
Clinical experts' plausible range	[redacted]	[redacted]
Revised company base case (adjustment factor of 2): stratified Weibull	[redacted]	[redacted]
EAG pessimistic OS extrapolation (adjustment factor of 3.5 applied at 5 years)	[redacted]	[redacted]
EAG optimistic OS extrapolation (adjustment factor of 1.5 applied at 5 years)	[redacted]	[redacted]

CS=company submission; EAG=External Assessment Group; MTC=medullary thyroid cancer; OS=overall survival; *RET*=rearranged during transfection
Source: Eli Lilly data on file[23]; company clarification model

Best supportive care

OS estimates for patients treated with BSC were generated by a stratified Weibull distribution fitted to EXAM trial[46] (*RET* M918T-positive population) placebo arm data. The EAG considers the stratified Weibull distribution approximates the EXAM trial[46] placebo arm OS K-M data and generates OS estimates within the range suggested by the company clinical experts.

Cabozantinib

The company generated cabozantinib OS estimates by applying a HR (EXAM trial[46], *RET*-mutant MTC population) to the stratified Weibull distribution used to generate BSC OS estimates. Clinical advice to the EAG agreed with the company that cabozantinib is more effective for *RET* M918T-positive patients than for the overall *RET*-mutant MTC population, and therefore, using EXAM trial[46] *RET* M918T-positive subgroup data may over-estimate OS for patients treated with cabozantinib The EAG considers that the application of a HR is reasonable; for the EXAM trial[46] ITT population, there is no evidence that hazards are non-proportional for the comparison of cabozantinib versus placebo (CS, Appendix O, Figure 11).

In the company clarification base case analysis, 10-year OS estimates for patients treated with cabozantinib were slightly lower than the most likely values suggested by company clinical expert estimates. The EAG considers that applying the HR to the (BSC) stratified spline 1 knot distribution generates a 10-year OS estimate that is closer to the range of most likely values suggested by company clinical experts than the estimate generated by the (BSC) stratified Weibull distribution chosen by the company (Table 49). Applying the HR to the (BSC) stratified spline 1 knot distribution generates a 20-year OS estimate that is slightly above the range of most likely values suggested by company clinical experts than the estimate generated by the (BSC) stratified Weibull distribution. The EAG has therefore generated OS estimates for patients treated with cabozantinib by applying the EXAM trial[46] HR to the stratified spline 1 knot distribution. Varying the stratified spline 1 knot distribution in the PSA results in implausible cabozantinib QALY values; the EAG has therefore excluded cabozantinib OS from the PSA.

Table 49 Cabozantinib OS estimates: *RET*-mutant MTC population

Distribution	10-year survival	20-year survival
Clinical experts' most likely value	[redacted]	[redacted]
Clinical experts' plausible range	[redacted]	[redacted]
Revised company base case: stratified Weibull	[redacted]	[redacted]
EAG preferred: stratified spline 1 knot	[redacted]	[redacted]

CS=company submission; EAG=External Assessment Group; MTC=medullary thyroid cancer; OS=overall survival
Source: CS, Table 66 and company clarification model

The OS extrapolations used in the company clarification base and EAG scenarios are presented in Figure 2.

Figure 2 Company clarification base case and EAG OS extrapolations for *RET*-mutant MTC population

BSC=best supportive care; EAG=External Assessment Group; K-M=Kaplan-Meier; MTC=medullary thyroid therapy; OS=overall survival; *RET*=rearranged during transfection
Source: Company clarification model

Post-progression survival

In the original company base case analysis, treatment with selpercatinib was associated with large incremental post-progression survival gains ([redacted] years versus cabozantinib and [redacted] years versus BSC). The company revised selpercatinib OS estimates reduced incremental post-progression-survival estimates (Table 50). In response to Clarification Question B5, the company claimed that patients may live for several years after progression (despite having no active subsequent treatment) and that there are differences in post-progression survival depending on treatment received prior to progression and referenced a German real-world

study[71] that included patients treated with cabozantinib and vandetanib as supporting evidence.

The EAG considers that the German real-world study[71] does not provide useful supporting evidence as:

- of the 46 German real-world study[71] patients with MTC, only six patients had a known *RET*-mutation; it is not clear how generalisable results from this study are to the population that is the focus of this appraisal
- 83% of patients in the German real-world study[71] received multiple lines of treatment with TKIs. In contrast, the company model patients only receive one line of kinase inhibitor treatment; it is assumed that patients do not receive any subsequent therapy
- 41 German real-world study[71] patients received vandetanib as a first-line treatment, whereas only seven patients received cabozantinib as a first-line treatment. This means that results from a comparison of post-progression survival of patients who received these two treatments are highly uncertain.

Compared to treatment with cabozantinib and BSC, a modest gain in post-progression survival for patients treated with selpercatinib may be expected due i) to the significant tumour response (reduction) experienced pre-progression and ii) as observed in the LIBRETTO-001 trial, treatment with selpercatinib is modelled to continue for a short duration after progression. However, it is unclear whether the post-progression survival estimated in the company model for patients treated with selpercatinib is clinically plausible.

Table 50 Company clarification base case analysis post-progression survival: *RET*-mutant MTC population

Treatment	Post-progression survival (undiscounted, years)	Difference (selpercatinib vs comparators)	Proportion of total life year gain (undiscounted) accrued in PD state
Selpercatinib	[redacted]	-	[redacted]%
Cabozantinib	2.20	[redacted]	57.59%
BSC	2.29	[redacted]	77.36%

BSC=best supportive care; MTC=medullary thyroid cancer; PD=progressed disease; *RET*=rearranged during transfection
Source: Company clarification model

6.2.2 *RET* fusion-positive TC population

The company fitted 20 different distributions to:

- LIBRETTO-001 trial (any-line *RET* fusion-positive) selpercatinib OS data (n=65)
- SELECT trial[25] lenvatinib OS data (n=261)
- SELECT trial[25] placebo arm RPFST-adjusted OS data (n=131).

The company generated AIC and BIC statistics using combined selpercatinib, lenvatinib and BSC OS data and concluded that none of the models fitted the data substantially better than any of the other models. Therefore, the company asked UK clinical experts to provide

estimates, at different landmark timepoints, of the proportions of patients anticipated to be alive following treatment.

Selpercatinib

In response to Clarification Question B2, the company considered that the piecewise exponential distribution OS estimates broadly aligned with clinical expert landmark OS estimates. However, to make the approach consistent with the approach used to generate OS estimates for patients with *RET*-mutant MTC, the company applied an adjustment factor of 1.2 at 5 years so that model OS estimates aligned even more closely with clinical expert estimates (Table 51).

The EAG considers that the adjustment factor applied by the company to the piecewise exponential distribution does not generate OS estimates that approximate the LIBRETTO-001 trial selpercatinib OS K-M data after 18 months (Figure 3). The EAG has implemented two alternative approaches to generating selpercatinib OS estimates (see Table 51). The EAG considers that the pessimistic OS extrapolation provides a better visual fit to the LIBRETTO-001 trial OS K-M data than the company base case distribution. However, the EAG cautions that OS estimates for all treatments are highly uncertain as they are estimated using results from naïve, unadjusted indirect comparisons.

Table 51 Selpercatinib OS estimates: *RET* fusion-positive TC population

Distribution	10-year survival	20-year survival
Clinical experts' most likely value	[redacted]	[redacted]
Clinical experts' plausible range	[redacted]	[redacted]
Revised company base case: piecewise exponential with adjustment factor of 1.2	[redacted]	[redacted]
EAG pessimistic OS extrapolation (adjustment factor of 1.5 applied from 18 months)	[redacted]	[redacted]
EAG optimistic OS extrapolation (adjustment factor of 0.9 applied from 60 months)	[redacted]	[redacted]

OS=overall survival; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Eli Lilly data on file[23]; company clarification model

Figure 3 Company base case and EAG OS extrapolations for *RET* fusion-positive TC population

Source: Company clarification model

Post-progression survival

In the original company base case, treatment with selpercatinib was associated with an incremental post-progression survival gain of [redacted] years versus lenvatinib and [redacted] years versus BSC. The adjustment to the distribution used to generate OS estimates for patients treated with selpercatinib OS (company clarification base case) only had a small impact on incremental post-progression-survival estimates (Table 52). However, it is unclear whether the post-progression survival estimated in the company model for patients treated with selpercatinib is clinically plausible.

Table 52 Company clarification base case analysis post-progression survival estimates: *RET* fusion-positive TC population

Treatment	Post-progression survival (undiscounted, years)	Difference (selpercatinib vs comparators)	Proportion of total life year gain (undiscounted) accrued in PD health state
Selpercatinib	[redacted]	-	[redacted]%
Lenvatinib	2.62	[redacted]	54.47%
BSC	2.05	[redacted]	82.00%

BSC=best supportive care; PD=progressed disease; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Company clarification model

6.3 *Progression-free survival*

6.3.1 *RET*-mutant MTC population

The company fitted 19 parametric distributions to:

- the selpercatinib PFS MAIC weighted curve (effective sample size=157)

- unweighted EXAM trial[45] K-M PFS data for the *RET*-mutant subgroup receiving cabozantinib (n=107)
- unweighted EXAM trial[45] K-M PFS data for the *RET*-mutant subgroup receiving placebo (n=62).

The company followed the same distribution selection process as used to select distributions to generate OS estimates (Section 6.2.1). The company concluded that statistical fit was relatively similar across all parametric distributions and therefore, to select the most appropriate distribution, assessed the clinical plausibility of the distributions. The company selected the (unstratified) loglogistic distribution to model PFS for all treatments as long-term PFS estimates aligned most closely with estimates provided by the company clinicians.

As with OS, there are substantial differences in statistical fit across the fitted distributions; the loglogistic distribution ranks poorly; differences in AIC and BIC between the loglogistic distribution and the best-fitting distribution are [redacted] and [redacted], respectively (CS, Table 60). The EAG considers that the loglogistic distribution approximates the K-M PFS data for each treatment reasonably well and provides clinically plausible long-term PFS estimates for all treatments but notes that there is evidence of non-proportional hazards for selpercatinib versus cabozantinib (CS, Appendix O, Figure 10 and Table 77), therefore an unstratified (jointly fitted) model may not be appropriate. However, the EAG notes that stratified distributions fitted by the company (which allow non-proportional hazards) generate clinically implausible estimates of PFS for at least one of the three treatments.

6.3.2 *RET* fusion-positive TC population

The company fitted 20 parametric distributions to:

- LIBRETTO-001 trial (any-line *RET* fusion-positive) selpercatinib OS data (n=65)
- SELECT trial[37] lenvatinib PFS data (n=261)
- SELECT trial[37] placebo arm PFS data (n=131).

The company followed the same distribution selection process as undertaken for OS (Section 6.2.2). The company considered that stratified models were appropriate as analyses presented in TA535[25] showed that hazards were not proportional across the majority of SELECT trial[37] survival outcomes. The company concluded that AIC and BIC statistics were similar across all distributions and therefore, to select the most appropriate distribution, the company assessed the clinical plausibility of distributions. The company selected the stratified Weibull distribution to model PFS for all treatments as long-term PFS estimates aligned most closely with estimates provided by the company clinicians.

There are substantial differences in statistical fit across the fitted distributions; the stratified Weibull distribution ranks poorly; differences in AIC and BIC between the stratified Weibull

distribution and the best-fitting distribution are [redacted] and [redacted] respectively (CS, Table 69). The EAG considers that the stratified Weibull distribution approximates the K-M PFS data for each treatment and generates PFS estimates in line with those elicited from company clinicians for patients treated with lenvatinib and BSC. The stratified Weibull distribution slightly underestimates long-term PFS estimates for patients treated with selpercatinib but generates the closest estimates of all the fitted stratified distributions.

6.4 *Dose adjustments*

In the company model, an RDI multiplier was used to reflect dose reductions due to treatment toxicity. The company assumed that patients treated with cabozantinib or lenvatinib received the recommended dose (140mg and 24mg once daily, respectively) in the first four model cycles; a mean RDI multiplier was applied from Week 5 onwards. Cabozantinib and lenvatinib have a flat price for all recommended doses and therefore treatment costs should have been adjusted for dose adherence (the proportion of days on which people had treatment) rather than RDI, as preferred by the NICE TA928[1] Appraisal Committee. Adherence data used in TA928[1] are redacted; adherence data may become available from the LIBRETTO-531 trial.[32] Data currently available from the LIBRETTO-531 trial[32] suggest that the proportion of patients with at least one dose interruption is substantially higher for patients treated with cabozantinib (81.9%) than for patients treated with selpercatinib (56.0%). In the absence of cabozantinib (and lenvatinib) adherence data, the EAG considers that the company use of RDI as a proxy for adherence is reasonable.

6.5 *Utility values*

During TA742,[29] the company mapped LIBRETTO-001 trial EORTC-QLQ-C30 data to EQ-5D data. This approach resulted in highly implausible results (a utility value of >[redacted] for pre- and post-progression in all subgroups tested). The NICE TA742[29] AC ultimately preferred the utility values used in TA516[21] and TA535;[25] these values were sourced from a vignette study conducted by Fordham 2015[56] (Table 53).

The company has used the Fordham 2015[56] utility values; these do not align with the NICE Reference Case[57] as these values were elicited from a sample (n=100) of the UK general population. The Fordham 2015[56] utility value used to model HRQoL in the progression-free health state appears quite high (0.8) and is close to age and sex-matched general population utility values (*RET*-mutant MTC population: 0.845; *RET* fusion-positive TC population: 0.857).[64]

The Fordham 2015[56] utility value used by the company to model HRQoL in the progressed-disease health state is very low (0.5). Clinical advice to the EAG is that patient HRQoL declines

significantly during the last 6 months of life. The EAG therefore considers that, due to the length of time patients remain in the progressed-disease health state, the model should have included time to death utilities. However, the EAG recognises that this approach would require a substantial restructuring of the company model and would not address uncertainty around the magnitude of any currently available utility values for patients with *RET*-mutant MTC or *RET* fusion-positive TC.

The EAG agrees with the company that the health state utility values generated by mapping LIBRETTO-001 trial any-line *RET*-mutant MTC population EORTC-QLQ-C30 data are not plausible as the progressed disease health state utility values are higher than the progression-free health state utility values (CS, Table 81). The EAG alternative approach used *RET* fusion-positive TC population health state utility values mapped (Young 2015[72] algorithm) from EORTC-QLQ-C30 data to EQ-5D data (Table 53). The EAG considers these health state utility values are more appropriate than the Fordham 2015[56] values as they are derived from LIBRETTO-001 trial HRQoL data and more accurately reflect the length of time patients spend in the model progressed disease health state. However, the EAG acknowledges that these utility values are derived from a small number of patients (n=[redacted] for progression-free; n=[redacted] for progressed disease). The EAG alternative health state utility values were used to model utility for patients with *RET*-mutant MTC and patients with *RET* fusion-positive TC.

Table 53 Health state utility values in company model

Health state	Mean health state utility value (SE)			
	Company base case	Source	EAG preferred	Source
Progression-free	0.80 (0.02)	Fordham 2015[56]	[redacted] ([redacted])	LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population) mapped to EQ-5D using Young 2015[72] algorithm
Progressed disease	0.50 (0.03)		[redacted] ([redacted])	

CS=company submission; EAG=External Assessment Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; *RET*=rearranged during transfection; SE=standard error
Source: CS, Table 81 and Table 84 (SEs sourced from company clarification model)

PSA: utility values

Due to the small number of patients (n=[redacted]; [redacted] assessments) informing the progressed disease health state utility value, the parameters were ordered within the probabilistic sensitivity analysis, using the difference method approach[73] to ensure sampled progression-free health state utility values remained higher than sampled progressed disease health state utility values.

6.6 *Severity modifier*

The company clarification response included revised QALY weight calculations (company response to clarification, Appendix A.1, Table 21). The company did not present any revised cost effectiveness results that included the application of a severity modifier (company response to clarification, Appendix A.2 to A.4).

RET-mutant MTC population

The company considered that, for the *RET*-mutant MTC population, it was appropriate to use a 1.2 severity modifier for the comparison of selpercatinib versus cabozantinib and versus BSC. The EAG was able to replicate the company results.

***RET* fusion-positive population**

The company considered that, for the *RET* fusion-positive population, it was only appropriate to use a 1.2 severity modifier for the comparison of selpercatinib versus BSC. The EAG was able to replicate the company results.

6.7 *Impact of EAG amendments on company base case results*

6.7.1 *RET*-mutant MTC population

The EAG has made the following revisions to the company base case *RET*-mutant MTC population cost effectiveness analysis:

- stratified spline 1 knot distribution to extrapolate cabozantinib OS (R1)
- mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population) (R2)
- pessimistic selpercatinib OS extrapolation using an adjustment factor of 3.5 applied at 5 years (R3)
- optimistic selpercatinib OS extrapolation using an adjustment factor of 1.5 applied at 5 years (R4)

Details of EAG revisions to the company model are presented in Appendix 8.6 of this EAG report. Deterministic cost effectiveness results for the *RET*-mutant MTC population are provided in Table 55 (versus cabozantinib) and Table 57 (versus BSC). Probabilistic cost effectiveness results for pairwise comparisons are presented in Table 56 and Table 58. Fully incremental analyses of probabilistic cost effectiveness results for the revised company base case and EAG alternative scenario are presented in Table 59 and Table 60 respectively. All results have been generated using list prices for all drugs except for selpercatinib (PAS price). Table 55, Table 56, Table 59 and Table 60 have been replicated in the confidential appendix but with the analyses including all confidential commercial arrangements as described in Table 54.

Table 54 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Selpercatinib	Simple PAS discount
Cabozantinib	Simple PAS discount
Lenvatinib	Simple PAS discount

PAS=Patient Access Scheme

Table 55 Deterministic results for the *RET*-mutant MTC population (selpercatinib versus cabozantinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier where relevant)	£/QALY (x1.2 modifier where relevant)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£89,900**	**2.080**	[redacted]	[redacted]	**£29,713***	**-**
R1) Stratified spline 1 knot distribution to extrapolate cabozantinib OS	[redacted]	[redacted]	£90,573	2.206	[redacted]	[redacted]	£36,666	£6,953
R2) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£89,900	2.417	[redacted]	[redacted]	£35,306	£5,593
R3) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£89,900	2.080	[redacted]	[redacted]	£36,554*	£6,841
R4) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£89,900	2.080	[redacted]	[redacted]	£27,047*	-£2,666
B. EAG alternative scenario (R1-R2)	[redacted]	[redacted]	**£90,573**	**2.594**	[redacted]	[redacted]	**£36,791**	**£7,078**
C. EAG exploratory scenarios								
C1. R1-R3	[redacted]	[redacted]	**£90,573**	**2.594**	[redacted]	[redacted]	**£49,853**	**£20,140**
C2. R1-R2, R4	[redacted]	[redacted]	**£90,573**	**2.594**	[redacted]	[redacted]	**£31,997**	**£2,284**

*1.2x severity modifier applied
EAG=External Assessment Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection

Table 56 Probabilistic results for *RET*-mutant MTC population (selpercatinib versus cabozantinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case (A.1)
A.1 Company clarification base case (1.2 severity modifier applied)	[redacted]	[redacted]	**£89,785**	**2.107**	[redacted]	[redacted]	**£29,877**	**-**
A.2 Company clarification base case (no modifier)	[redacted]	[redacted]	**£89,785**	**2.107**	[redacted]	[redacted]	**£35,852**	**-**
B. EAG alternative scenario (R1-R2)	[redacted]	[redacted]	**£90,720**	**2.673**	[redacted]	[redacted]	**£36,831**	**£6,955**
C. EAG exploratory scenarios								
C1. R1-R3	[redacted]	[redacted]	**£90,666**	**2.662**	[redacted]	[redacted]	**£50,540**	**£20,664**
C2. R1-R2, R4	[redacted]	[redacted]	**£90,636**	**2.658**	[redacted]	[redacted]	**£32,232**	**£2,356**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection

Table 57 Deterministic results for *RET*-mutant MTC population (selpercatinib versus BSC), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£17,089**	**1.508**	[redacted]	[redacted]	**£39,481**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£17,089	1.908	[redacted]	[redacted]	£39,689	£209
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£17,089	1.508	[redacted]	[redacted]	£47,376	£7,895
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£17,089	1.508	[redacted]	[redacted]	£36,260	-£3,220
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£17,089**	**1.908**	[redacted]	[redacted]	**£39,689**	**£209**
C. EAG exploratory scenarios								
C1. R1-R2	[redacted]	[redacted]	**£17,089**	**1.908**	[redacted]	[redacted]	**£51,150**	**£11,669**
C2. R1, R3	[redacted]	[redacted]	**£17,089**	**1.908**	[redacted]	[redacted]	**£35,141**	**-£4,340**

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

Table 58 Probabilistic results for *RET*-mutant MTC population (selpercatinib versus BSC), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY QALYs (x1.2 modifier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£17,110**	**1.516**	[redacted]	[redacted]	**£39,458**	**-**
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£17,164**	**1.919**	[redacted]	[redacted]	**£39,147**	**-£311**
C. EAG exploratory scenarios								
C1. R1-R2	[redacted]	[redacted]	**£17,122**	**1.913**	[redacted]	[redacted]	**£50,781**	**£11,323**
C2. R1, R3	[redacted]	[redacted]	**£17,080**	**1.928**	[redacted]	[redacted]	**£35,075**	**-£4,382**

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection

Table 59 Company clarification base case probabilistic results (fully incremental analysis) for *RET*-mutant MTC population, no severity modifiers applied, PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER per QALY gained
BSC	£17,110	1.52	-
Cabozantinib	£89,785	2.11	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£47,349

BSC=best supportive care; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life years; *RET*=rearranged during transfection
Source: Company clarification response, Table 24

Table 60 EAG alternative scenario probabilistic results (fully incremental analysis) for *RET*-mutant MTC population, no severity modifiers applied, PAS price for selpercatinib*

Treatment	Total costs	Total QALYs	ICER per QALY gained
BSC	£17,164	1.919	-
Cabozantinib	£90,720	2.673	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£46,980

* No modifiers applied when calculating ICERs per QALY gained; however, the comparison of selpercatinib versus BSC is eligible for a 1.2x modifier
BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life years; *RET*=rearranged during transfection
Source: Company clarification model with EAG revisions

6.7.2 *RET* fusion-positive TC population

The EAG has made the following revisions to the company base case *RET* fusion-positive TC population cost effectiveness analysis:

- mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population (R1)
- pessimistic selpercatinib OS extrapolation using an adjustment factor of 1.5 applied at 18 months (R2)
- optimistic selpercatinib OS extrapolation using an adjustment factor of 0.9 applied at 5 years (R3).

Details of the EAG revisions to the company model are presented in Appendix 7, Section 8.7 of this EAG report. Deterministic cost effectiveness results for the *RET* fusion-positive TC population are provided in Table 61 (versus lenvatinib) and Table 63 (versus BSC). Probabilistic cost effectiveness results for the pairwise comparisons are presented in Table 62 and Table 64. Fully incremental analyses of probabilistic cost effectiveness results for the revised company base case and EAG alternative scenario are presented in Table 65 and Table 66 respectively. All results have been generated using list prices for all drugs except for selpercatinib (PAS price). Table 55, Table 56, Table 59 and Table 60 have been replicated in the confidential appendix but with the analyses including all confidential commercial arrangements as described in Table 54.

Table 61 Deterministic results for *RET* fusion-positive TC population (selpercatinib versus lenvatinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£96,507**	**2.622**	[redacted]	[redacted]	**£36,329**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£96,507	2.988	[redacted]	[redacted]	£35,130	-£1,199
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£96,507	2.622	[redacted]	[redacted]	£46,063	£9,734
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£96,507	2.622	[redacted]	[redacted]	£32,221	-£4,108
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£96,507**	**2.988**	[redacted]	[redacted]	**£35,130**	**-£1,199**
C. EAG exploratory scenarios								
C1. (R1-R2)	[redacted]	[redacted]	**£96,507**	**2.988**	[redacted]	[redacted]	**£50,131**	**£13,802**
C2. (R1, R3)	[redacted]	[redacted]	**£96,507**	**2.988**	[redacted]	[redacted]	**£29,756**	**-£6,573**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 62 Probabilistic results for *RET* fusion-positive TC population (selpercatinib versus lenvatinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£96,510**	**2.631**	[redacted]	[redacted]	**£36,347**	**-**
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£96,490**	**2.974**	[redacted]	[redacted]	**£35,462**	**-£885**
C. EAG exploratory scenarios								
C1. R1-R2	[redacted]	[redacted]	**£96,512**	**3.000**	[redacted]	[redacted]	**£50,410**	**£14,063**
C2. R1, R3	[redacted]	[redacted]	**£96,533**	**2.955**	[redacted]	[redacted]	**£30,147**	**-£6,199**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 63 Deterministic results for *RET* fusion-positive TC population (selpercatinib versus BSC), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£16,030**	**1.272**	[redacted]	[redacted]	**£37,050**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£16,030	1.645	[redacted]	[redacted]	£36,312	-£738
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£16,030	1.272	[redacted]	[redacted]	£43,021	£5,971
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£16,030	1.272	[redacted]	[redacted]	£34,138	-£2,912
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£16,030**	**1.645**	[redacted]	[redacted]	**£36,312**	**-£738**
C. EAG exploratory scenarios								
C1. R1-R2	[redacted]	[redacted]	**£16,030**	**1.645**	[redacted]	[redacted]	**£45,285**	**£8,235**
C2. R1, R3	[redacted]	[redacted]	**£16,030**	**1.645**	[redacted]	[redacted]	**£32,368**	**-£4,681**

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 64 Probabilistic results for *RET* fusion-positive TC population (selpercatinib versus BSC), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		BSC		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£15,983**	**1.277**	[redacted]	[redacted]	**£37,025**	**-**
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£16,020**	**1.643**	[redacted]	[redacted]	**£36,650**	**-£375**
C. EAG exploratory scenarios								
C1. R1-R2	[redacted]	[redacted]	**£16,056**	**1.655**	[redacted]	[redacted]	**£45,389**	**£8,365**
C2. R1, R3	[redacted]	[redacted]	**£16,068**	**1.629**	[redacted]	[redacted]	**£32,792**	**-£4,232**

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=patient access scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 65 Company clarification base case probabilistic results (fully incremental analysis) for *RET* fusion-positive TC population, no modifiers applied, PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER per QALY gained
BSC	£15,983	1.28	-
Lenvatinib	£96,510	2.63	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£44,429

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Company clarification response, Table 30

Table 66 EAG alternative scenario probabilistic results (fully incremental analysis) for *RET* fusion-positive TC population, no modifiers plan, PAS price for selpercatinib*

Treatment	Total costs	Total QALYs	ICER per QALY gained
BSC	£16,020	1.643	
Lenvatinib	£96,490	2.974	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£43,983

* No modifiers applied when calculating ICERs per QALY gained; however, the comparison of selpercatinib versus BSC is eligible for a 1.2x modifier
BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Company clarification model with EAG revisions

6.8 *Cost effectiveness conclusions*

6.8.1 *RET*-mutant MTC population

The EAG alternative probabilistic (deterministic) ICER for the comparison of selpercatinib versus cabozantinib is £36,831 (£36,791) per QALY gained and versus BSC is £39,147 (£39,689) per QALY gained.

For both comparisons, the biggest driver of cost effectiveness is OS. The EAG considers there is currently no robust clinical effectiveness evidence to reliably estimate OS gains for patients treated with selpercatinib versus cabozantinib and versus BSC. More robust data will become available from the LIBRETTO-531 trial.

6.8.2 *RET* fusion-positive TC

The EAG alternative probabilistic (deterministic) ICER for the comparison of selpercatinib versus lenvatinib is £35,462 (£35,130) per QALY gained and versus BSC is £36,650 (£36,312) per QALY gained.

For both comparisons, the biggest driver of cost effectiveness is OS. The EAG considers there is currently no robust clinical effectiveness evidence to reliably compare OS for patients treated with selpercatinib, lenvatinib and BSC. The EAG is unaware of any additional evidence being collected from systematic therapy naïve patients with *RET* fusion-positive TC being treated with selpercatinib.

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8 APPENDICES

8.1 *Appendix 1: LIBRETTO-321 trial*

The EAG agrees with the company that the LIBRETTO-321 trial provides less relevant and less robust evidence than the LIBRETTO-001 trial (due to its location [China] and sample size [n=29 for *RET*-mutant MTC and n=1 for RET fusion-positive TC]). However, the EAG considers that as the LIBRETTO-321 trial reports data for patients with selpercatinib, it provides relevant supportive evidence.

8.1.1 LIBRETTO-321 trial: trial characteristics

The LIBRETTO-321 trial was an open-label, phase II trial conducted in 15 centres across China. It enrolled patients aged ≥18 years with advanced solid tumours, including *RET*-mutant MTC and *RET* fusion-positive solid tumours (TC and NSCLC). Patients (n=77) were enrolled from March 2020 to March 2021 and included 29 patients with *RET*-mutant MTC (26 patients had their *RET mutation* status centrally confirmed and were included in the primary analysis set) and 1 patient with *RET* fusion-positive TC. Patients were permitted to have received prior systemic therapy (excluding selective *RET* inhibitors). All patients received selpercatinib (160mg BID) every 28 days until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation. Patients were permitted to receive treatment with selpercatinib beyond disease progression if the clinician considered that the patient was continuing to benefit. The primary outcome was the proportion of patients in the primary analysis set with a confirmed ORR by IRC. Other key outcomes included DoR and PFS by IRC, OS and AEs.

8.1.2 LIBRETTO-321 trial: patient characteristics

All the patients in the LIBRETTO-321 trial were of Chinese Asian origin; the proportion of males in the LIBRETTO-321 trial was higher than in either the LIBRETTO-001 or LIBRETTO-531 trials. Patients in the LIBRETTO-321 trial are therefore less reflective of patients who would be treated in the NHS. Furthermore, as shown in Table 67, there was only 1 patient with *RET* fusion-positive TC in the LIBRETTO-321 trial and evidence for patients with *RET* fusion-positive TC from this trial are therefore very limited. This patient had papillary thyroid cancer.

Table 67 LIBRETTO-321 trial baseline characteristics of patients

Characteristic	*RET*-mutant MTC		*RET* fusion-positive TC
	Selpercatinib any-line primary analysis set (n=26[a])	Selpercatinib: any-line all patients (n=29[b])	Selpercatinib: kinase inhibitor-naïve (n=1)
Age, median (range) years	50 (23 to 70)	46 (23 to 70)	19
Age <18 years	NR	NR	0
Age 18 to <65 years	NR	NR	1
Age ≥65 years	NR	NR	0
Male, n (%)	20 (76.9)	23 (79.3)	0
Asian, n (%)	26 (100.0)	29 (100.0)	1
Stage IV disease	n/a	n/a	1
ECOG PS ≥1, n (%)	11 (42.3)	17 (58.6)	0
RET mutation M918T	20 (76.9)	22 (75.9)	n/a
Patients with measurable disease, n (%)	26 (100.0)	27 (93.1)	NR
Received prior kinase inhibitor, n (%)	4 (15.4)	7 (24.1)	0
Received any prior systemic therapy, n (%)	9 (34.6)	12 (41.4)	0

[a] Patients with *RET*-mutant MTC whose *RET mutation* status was confirmed by central laboratory; TC=thyroid cancer subtypes that develop in follicular cells
[b] All enrolled patients with *RET*-mutant MTC

n/a=not applicable; NR=not reported; RET=rearranged during transfection
ECOG PS=Eastern Cooperative Oncology Group performance status; n/a=not applicable; NR=not reported; RET=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Zheng 2022[44] and ClinicalTrials.gov[74]

8.1.3 LIBRETTO-321 trial: efficacy results

IRC-assessed ORR results were reported for the following populations of patients with *RET*-mutant MTC in the LIBRETTO-001 trial:

- cabozantinib/vandetanib-naïve primary analysis set/all patients (n=17)
- any-line primary analysis set (n=26)
- any-line all patients with MTC (n=29)

For all populations, ORRs were similar, ranging from 57.7% in the any-line primary analysis set to 58.8% in the cabozantinib/vandetanib-naïve population. As in the LIBRETTO-001 trial, median DoR was not reached in any population, nor was median IRC-assessed PFS or OS. At a median follow-up of 8.7 months, 93.3% of responses in the any-line primary analysis set were ongoing.

The LIBRETTO-321 trial ORRs were notably lower than those reported for patients with *RET*-mutant MTC in the LIBRETTO-001 trial. This may be due to differences in patient characteristics of patients between the LIBRETTO-001 and LIBRETTO-321 trials (the most notable of which were the proportion of patients who were classified as Asian and the proportion of patients who were male, see Section 3.4 and Section 8.1.2 of this EAG report) and/or that LIBRETTO-321 trial[44] data has shorter follow-up than LIBRETTO-001 trial[31] data.

Only one patient with *RET* fusion-positive TC was included in the LIBRETTO-321. This patient was treated for 23.4 weeks and achieved a PR at Week 8 that was still ongoing at 25 March 2021 DCO.

8.1.4 LIBRETTO-321 trial HRQoL results: *RET*-mutant MTC

HRQoL data were collected during the LIBRETTO-321 trial using the EORTC QLQ-C30 and the mSTIDAT for *RET*-mutant MTC patients only. HRQoL data were available for Cycle 3, Cycle 5, Cycle 7, Cycle 9 and Cycle 13.

EORTC QLQ-C30

At Cycle 9 (the EAG presented these data to match the LIBRETTO-001 trial time point), data were only available for 12 patients. All patients with *RET*-mutant MTC reported either a clinically meaningful improvement in (75%) or stable (25%) global health status/QoL subscale score. Similarly, most (>90%) patients reported clinically meaningful improvements or stable scores for EORTC QLQ-C30 symptom subscale items.

mSTIDAT bowel diaries

At baseline, a smaller proportion of patients (n=5/29, 17.2%) with *RET*-mutant MTC reported diarrhoea in the LIBRETTO-321 trial than in the LIBRETTO-001 trial. Four patients reported mild diarrhoea and one patient reported moderate diarrhoea at baseline. At Cycle 5, four patients reported no diarrhoea and one patient reported mild diarrhoea.

8.1.5 LIBRETTO-321 trial: safety results

LIBRETTO-321 trial safety results were only reported for all 77 trial patients (i.e., not reported separately for patients with *RET*-mutant MTC or *RET* fusion-positive TC).

8.2 *Appendix 2: EAG assessment of the statistical approaches used by the company to analyse LIBRETTO-001 trial and LIBRETTO-531 trial data*

A summary of the EAG checks of the pre-planned statistical approaches used by the company to analyse data from the LIBRETTO-001 and LIBRETTO-531 trials is provided in Table 68.

Table 68 EAG assessment of the statistical approaches used by the company to analyse LIBRETTO-001 trial and LIBRETTO-531 trial data

Item	LIBRETTO-001		LIBRETTO-531	
	EAG assessment	Statistical approach with EAG comments	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Partial	The analysis populations of the LIBRETTO-001 trial were clearly defined in Table 5 of the CS. The analysis sets were also provided in the TSAP version 3 (TSAP v3, Section 2), although the EAG notes that version 3 of the TSAP is dated 19th December 2022 (after the date of the first DCO), and the purpose of this update to the TSAP was to define the analysis set for the final clinical study report. The EAG considers that the company's efficacy analysis sets for the final CSR were appropriate, but considers that is unclear why these efficacy analysis sets were not pre-specified in the TSAP version 1 (company response to NICE's clarification letter, question A6)	Partial	The efficacy analysis set was not confirmed in the CS or Hadoux 2023, and the CSR was unavailable at the time of the company's response to NICE's clarification letter (question C1). In the TSAP (version 3) it was stated that all efficacy analyses would be performed using the ITT population (all randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol; patients analysed according to the treatment arm they were assigned to regardless of what treatment they received). It was stated in Hadoux 2023 that all analyses were conducted in accordance with the TSAP. Safety analyses were performed with data from all patients who underwent randomization and received at least one dose of trial treatment (Hadoux 2023). The safety analysis set was pre-defined in the TSAP (TSAP v3, Section 7)
Was an appropriate sample size calculation pre-specified?	Yes	Sample size and design considerations of phase I and phase II of the LIBRETTO-001 trial were outlined in Table 17 of the CS, and were pre-specified (protocol v8, Section 8.3 and TSAP v1, Section 4). The EAG is satisfied that designs and sample sizes were appropriate for the dose escalations and dose expansion objectives of phase I and phase II, respectively, of the LIBRETTO-001 trial	Yes	The sample size calculation of the LIBRETTO-531 trial was provided in the Hadoux 2023 paper. The sample size calculation was pre-specified in the TSAP (TSAP v3, Section 6). The EAG considers that the sample size calculation was appropriate
Were all protocol amendments made prior to analysis?	Partial	A summary of changes from version 1 to version 8 (the latest version, 10th June 2019) of the LIBRETTO-001 protocol were provided as a supplementary document to the Drilon 2018 publication The EAG considers that all protocol amendments were appropriate and notes that all were made prior to the first DCO date (17th June 2019)	Yes	A summary of amendments to the protocol of the LIBRETTO-531 trial were provided alongside the latest version of the protocol (amendment h). All amendments were appropriate and made prior to the date of the first DCO (22 May 2023). A summary of amendments to the TSAP of the LIBRETTO-531 trial were provided alongside the latest version of the TSAP (TSAP v3). All amendments were appropriate and made prior to the date of the first DCO (22 May 2023)

Item	LIBRETTO-001		LIBRETTO-531	
	EAG assessment	Statistical approach with EAG comments	EAG assessment	Statistical approach with EAG comments
		Some amendments to the TSAP were made after the date of the first data-cut off. The analysis set for the final clinical study report was defined in TSAP version 3 (dated 19th December 2022). See "Were all analysis populations clearly defined and pre-specified?"		
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary outcome of phase I of the LIBRETTO-001 trial was identification of the maximum-tolerated dose and the recommended phase II dose of selpercatinib and for phase II of the LIBRETTO-001 trial was ORR (CS, Table 6). Both primary outcomes were pre-defined (TSAP v1, Section 3.1; protocol version 8, Section 2.1). Secondary efficacy outcomes of phase I of the LIBRETTO trial included safety and tolerability, pharmacokinetic properties, and ORR, and of phase II of the LIBRETTO-001 trial included DoR, PFS and OS (CS, Table 6). Secondary outcomes were pre-defined (TSAP v1, Section 10; protocol version 8, Section 2.2). Appropriate statistical analysis methods for the primary and secondary efficacy outcomes were pre-specified (TSAP v1, Section 10)	Yes	The primary outcome of the LIBRETTO-531 trial was PFS, and secondary outcomes were TFFS, ORR, DoR, OS and PFS2 (CS, Appendix M, Table 62). All outcomes were pre-defined (TSAP, v3, Section 8). Statistical analysis methods for the primary and secondary efficacy outcomes were pre-specified (TSAP v3, Section 10). The EAG notes that Cox PH models were used to analyse time-to-event outcomes from the LIBRETTO-531 trial. The Cox PH model is only an appropriate analysis method if the assumption of PH holds, i.e., the event hazards associated with the intervention and comparator data are proportional over time. The results of PH assessments for the time-to-event outcomes presented in the CS (PFS, DoR, OS) were provided in the company response to NICE's clarification letter (question A13). The company considered that the PH assumption appears to hold for OS, PFS and DOR; the EAG agrees with the company's assessments of PH. The company employed a multiple testing strategy, and at the time of the interim analysis, statistical significance for PFS was determined if the two-sided P value was less than 0.003. TFFS was to be tested against a two-sided significance level of 0.05 only if the results for PFS were significant (Hadoux 2023). Other outcomes were not accounted for in the multiple testing strategy, and p-values should not be used to infer statistical significance. An overview of the multiple testing strategy was pre-specified (TSAP v3 Section 8.8), with full details provided in the Adaptive Design Charter (not available to the EAG). The EAG considers that the general approach to multiple testing seems to be reasonable, but was unable to verify all details

Item	LIBRETTO-001		LIBRETTO-531	
	EAG assessment	Statistical approach with EAG comments	EAG assessment	Statistical approach with EAG comments
Was the analysis approach for PROs appropriate and pre-specified?	Partial	An exploratory endpoint of phase II of the LIBRETTO-001 trial was pre-specified as change from baseline in disease-related symptoms and HRQoL as measured by EORTC QLQ-C30 (protocol v8, Section 8.1). The analysis approach was described in the CS (Table 18). To be eligible for the EORTC-QLQ-C30 analysis, treated patients were required to have a baseline assessment and at least one post-baseline assessment for the complete EORTC QLQ-C30 questionnaire, including all subscales (CS, 80). The EAG considers that the descriptive analysis approach was appropriate but notes that neither the analysis population nor the analysis approach were pre-specified in the protocol or TSAP	n/a	No PROs were presented in the CS for the LIBRETTO-531 trial
Was the analysis approach for AEs appropriate and pre-specified?	Yes	AEs were presented as numbers and percentages of patients experiencing events; no formal statistical analyses of AEs were conducted. Summaries of TEAEs occurring in ≥15% of patients, Grade 3-4 AEs occurring in ≥2% of patients and AEs of special interest were presented in the CS (CS pp126-131). The EAG is satisfied that the approach employed was pre-specified (protocol v8, Section 9) and appropriate	Yes	AEs were presented as numbers and percentages of patients experiencing events; no formal statistical analyses of AEs were conducted. A summary of TEAEs was provided in the CS (CS, Table 54) and a summary of AEs was provided in the CS, Appendix M (Table 66 and Table 67). The EAG is satisfied that the approach employed was pre-specified (TSAP v3, p35) and appropriate
Was a suitable approach employed for handling missing data?	Yes	No imputation of missing data was conducted within the LIBRETTO-001 trial, except for imputation of partial dates (TSAP v1, Section 7.1). The EAG agrees that it was appropriate not to conduct any data imputation and to present data as recorded. Censoring rules for time-to-event outcomes (DoR, PFS, OS) were appropriate and pre-specified (TSAP, Section 10)	Partial	The company's approach to handling missing data was appropriate and pre-specified in the TSAP (TSAP v3, pp29-30). Censoring rules for time-to-event outcomes (PFS, TFFS, DoR, OS, PFS2) were appropriate and were pre-specified for PFS, TFFS, OS and PFS2 (TSAP v3, pp21, 26, 33-34). Censoring rules were not pre-specified for DoR

Item	LIBRETTO-001		LIBRETTO-531	
	EAG assessment	Statistical approach with EAG comments	EAG assessment	Statistical approach with EAG comments
Were all subgroup and sensitivity analyses pre-specified?	Partial	For the cabozantinib/vandetanib-naïve *RET*-mutant MTC efficacy analysis set in LIBRETTO-001, the company presented subgroup analyses of ORR and DoR by demographics (CS, Table 33), by *RET* mutation type and type of molecular assay (CS, Table 34), and by number of prior therapy and type of prior therapy (CS, Table 35). All except type of molecular assay were pre-specified. For the systemic therapy-naïve *RET* fusion-positive TC analysis set, the company presented ORR and DoR by demographics (CS, Table 36 and Figure 25), by *RET* mutation type and type of molecular assay (CS, Table 37), by number of prior therapy and type of prior therapy (CS, Table 38 and Figure 25), and by tumour histology subtype CS, Figure 25). All presented subgroup analyses were pre-specified (TSAP v1, Section 10.10). No sensitivity analyses were presented in the CS	Yes	No subgroup analyses were presented in the CS. In the CS, Appendix M, results were presented from unstratified Cox regression models and unstratified log rank tests for both PFS and OS. These sensitivity analyses were pre-specified in the TSAP (TSAP v3, Section 8)

AE=adverse event; CS=company submission; CSR=clinical study report; DCO=data cut-off; DoR=duration of response; EAG=External Assessment Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire; HRQoL=health-related quality of life; ITT=intention-to-treat; MTC=medullary thyroid cancer; NICE=National Institute for Health and Care Excellence; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; PFS2=progression-free survival 2; PH=proportional hazards; *RET*=rearranged during transfection; TC=thyroid cancer; TEAE=treatment-emergent adverse event; TFFS=treatment failure-free survival; TSAP=trial statistical analysis plan
Source: CS, LIBRETTO-001 CSR (13th January 2023),[31] LIBRETTO-001 TSAP version 1[43] and version 3,[35] LIBRETTO-001 trial protocol version 8,[43] LIBRETTO-531 TSAP version 3,[32] LIBRETTO-531 trial protocol (amendment h),[32] Hadoux 2023[32]

8.3 *Appendix 3: Adverse events reported in the LIBRETTO-001 and LIBRETTO-531 trials*

8.3.1 LIBRETTO-001 and LIBRETTO-531 trial: *RET*-mutant MTC population, summary of AEs

A summary of reported AEs is presented in Table 69. A summary of the most common AEs (occurring in ≥50% patients in one of the LIBRETTO-001 trial selpercatinib treatment cohorts) and pre-specified AESIs are reported in Table 70. The data show that:

- for some general types of AEs (Table 69), most notably treatment-emergent and treatment-related SAEs and treatment-emergent fatal AEs, the incidence rates for patients with *RET*-mutant MTC and *RET* fusion-positive TC in the LIBRETTO-001 trial differed
- there were also some differences in frequencies between patients with MTC treated with selpercatinib in the LIBRETTO-001 trial and patients with MTC treated with selpercatinib in the LIBRETTO-531 trial (Table 69 and Table 70); frequencies of general and specific types of AEs were often lower in the LIBRETTO-531 trial than in the LIBRETTO-001 trial, in particular treatment emergent Grade ≥3 AEs, SAEs and the incidence of fatigue
- frequencies of general and specific types of AEs in the LIBRETTO-531 trial were also lower for patients treated with selpercatinib than for patients treated with physician's choice (Table 69 and Table 70).

Table 69 LIBRETTO-001 and LIBRETTO-531 trials: *RET*-mutant MTC population, summary of AEs

General type of AE	LIBRETTO-001 trial			LIBRETTO-531 trial	
	Selpercatinib Overall SAS n=837	Selpercatinib *RET*-mutant MTC SAS n=324	Selpercatinib *RET* fusion-positive TC SAS n=66	Selpercatinib *RET*-mutant MTC n=193	Physician's choice *RET*-mutant MTC n=97
TE-AE, n (%)	[redacted]	[redacted]	[redacted]	186 (96.4)	96 (99.0)
TR-AE, n (%)	[redacted]	[redacted]	[redacted]	173 (89.6)	95 (97.9)
Grade ≥3 TE-AE, n (%)	[redacted]	[redacted]	[redacted]	102 (52.8)	74 (76.3)
Grade ≥3 TR-AE, n (%)	[redacted]	[redacted]	[redacted]	72 (37.3)	66 (68.0)
TE-AE leading to permanent treatment discontinuation, n (%)	[redacted]	30 (9.3)	2 (3.0)	9 (4.7)	26 (26.8)
TR-AE leading to permanent treatment discontinuation, n (%)	[redacted]	17 (5.2)	1 (1.5)	4 (2.1)	22 (22.7)
TE-SAE, n (%)	[redacted]	[redacted]	[redacted]	42 (21.8)	26 (26.8)
TR-SAE, n (%)	[redacted]	[redacted]	[redacted]	11 (5.7)	17 (17.5)
Fatal TE-AE, n (%)	[redacted]	[redacted]	[redacted]	4 (2.1)	2 (2.1)
Fatal TR-AE, n (%)	[redacted]	[redacted]	[redacted]	1 (0.5) [a]	0 (0.0)

[a] The field of relationship to the trial drug was left blank by the investigator; the relationship was updated to "nonrelated" after the DCO date

AE=adverse event; CS=company submission; DCO=data-cut off; MTC=medullary thyroid cancer; RET=rearranged during transfection; SAE=serious adverse event; SAS=safety analysis set; TC=thyroid cancer originating in the follicular cells; TE=treatment-emergent; TR=treatment-related

Source: CS, Table 49, Table 54, Appendix F.2, Table 28

Table 70 LIBRETTO-001 and LIBRETTO-531 trials: *RET*-mutant MTC population, most common[a] TEAEs and all AESIs

Specific type of AE	LIBRETTO-001 trial			LIBRETTO-531 trial	
	Selpercatinib Overall SAS n=837	Selpercatinib *RET*-mutant MTC SAS n=324	Selpercatinib *RET fusion-positive* TC SAS n=66	Selpercatinib *RET*-mutant MTC n=193	Physician's choice *RET*-mutant MTC n=97
TEAEs [a]					
Oedema	[redacted]	[redacted]	[redacted]	NR [b]	NR [b]
Diarrhoea	[redacted]	[redacted]	36 (54.5)	51 (26.4)	59 (60.8)
Fatigue	[redacted]	[redacted]	[redacted]	36 (18.7)	21 (21.6)
Dry mouth	366 (43.7)	140 (43.2)	33 (50.0)	61 (31.6)	10 (10.3)
AESIs					
Hypertension	[redacted]	[redacted]	[redacted]	82 (42.5)	40 (41.2)
AST increase	316 (37.8)	118 (36.4)	[redacted]	46 (23.8)	37 (38.1)
ALT increase	305 (36.4)	107 (33.0)	[redacted]	51 (26.4)	33 (34.0)
ECG QT prolongation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]	NR	NR

[a] TEAEs occurring in ≥50% patients in one of the LIBRETTO-001 trial selpercatinib treatment cohorts
[b] Peripheral oedema reported in the LIBRETTO-531 trial
AE=adverse event; AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=alanine aminotransferase increased; CS=company submission; ECG=electrocardiogram; MTC=medullary thyroid cancer; NR=not reported; *RET*=rearranged during transfection; SAE=serious adverse event; SAS=safety analysis set; TC=thyroid cancer originating in the follicular cells; TEAE=treatment-emergent adverse event
Source: CS, Table 50, Table 53, Appendix F.2, Table 29, Appendix F.4, Table 32, Appendix M.3, Table 67

8.3.2 Hypertension reported in the LIBRETTO-001 trial

As highlighted in Section 3.9, hypertension is an AESI that particularly affects patients treated with selpercatinib. In the CS (pp129-130), it is reported that in the LIBRETTO-001 trial, the frequency of reported hypertension AEs by any grade was similar between patients with and without a history of hypertension. Data provided at clarification (Clarification Question A8) confirmed any grade AESIs of hypertension were similar regardless of history of hypertension for patients with *RET*-mutant MTC or *RET* fusion-positive TC treated with selpercatinib. Grade 3 hypertension was more commonly experienced by patients with a history of hypertension than those without. Grade 4 hypertension was only experienced by one patient; this patient had *RET*-mutant MTC.

Dose reductions and withheld doses for hypertension were not very common (i.e., occurred in <10% of patients) for patients with or without hypertension with either *RET*-mutant MTC or *RET* fusion-positive TC (CS, p130 and Clarification Question A9). Only [redacted] patient discontinued selpercatinib due to hypertension; this patient had *RET*-mutant MTC.

8.3.3 Diarrhoea reported in the LIBRETTO-001 trial

As highlighted in Section 3.9, diarrhoea is an AE that particularly affects patients with MTC and impacts on their quality of life. In the LIBRETTO-001 trial, a higher proportion of patients with *RET*-mutant MTC were reported to have diarrhoea at baseline ([redacted] in the cabozantinib/vandetanib-naïve MTC population and [redacted] in the any-line MTC population) than were reported to have it as an AE over the study period (see Table 70). The impact on quality of life is reported in Section 3.8.1.

8.4 *Appendix 4: Prognostic factors and effect modifiers that could not be adjusted for in the MAICs*

Prognostic factors and effect modifiers that were identified in the company's SLR, but could not be adjusted for in the MAICs are listed in the CS, Appendix D (Table 20) and reproduced below. These variables were not reported in the EXAM trial and/or the LIBRETTO-001 trial:

- macroscopically evident extrathyroidal extension
- tumour size
- post-operative calcitonin doubling time
- post-operative carcinoembryonic antigen doubling time
- RAS-mutation
- circulating *RET* M918T mutated tumour DNA
- CA19-9
- multiple endocrine neoplasia type 2
- CDKN2C copy number
- oestrogen receptor α expression
- vascular invasion
- multiple endocrine neoplasia syndrome type IIB
- perineural invasion
- PD-1, PD-L1
- CD133, CD44
- number of involved lymph nodes

8.5 *Appendix 5: Adverse events (EXAM, SELECT and DECISION trials)*

The proportions of patients experiencing the most common AEs in the EXAM, SELECT and DECISION trials are presented in Table 71 (active treatment arms) and Table 72 (placebo arms). The reported AEs relate to all patients for whom safety data were available, not only patients with *RET* alterations. Furthermore, only patients in the DECISION trial were systemic therapy-naïve. The frequency cut-off used for inclusion into Table 71 was >50% any-grade AEs and the frequency cut-off for inclusion into Table 72 was >20% any-grade AEs. The different cut-offs reflect the fact that more patients who received active treatment experienced AEs than patients who received no active treatment (i.e., the placebo arms).

Table 71 EXAM, SELECT and DECISION trials: Total and most common[a] AEs

Type of AE	MTC		TC			
	EXAM trial		SELECT trial		DECISION trial	
	Cabozantanib n=214		Lenvatinib n=261		Sorafenib n=207	
	Any-grade, %	Grade ≥3, %	Any-grade, %	Grade ≥3, %	Any-grade, %	Grade ≥3, %
All	99.5	69.2	99.6	85.4	98.6	64.3
Diarrhoea	70.1	21.5	59.4	8.0	68.6	5.8
Weight-loss	57.9	9.8	46.4	9.6	46.9	5.8
PPE syndrome	52.8	12.6	31.8	3.4	76.3	20.3
Fatigue/asthenia[b]	42.5	9.8	59.0	9.2	49.8	5.8
Hypertension	32.7	8.9	67.8	41.8	40.6	9.7

[a] Most common defined as any-grade AEs occurring in >50% of patients and Grade ≥3 AEs occurring in >10% of patients in any active treatment arm
[b] fatigue and asthenia reported separately for EXAM trial, only fatigue data reported in this table
AE=adverse event; PPE=palmar-plantar erythrodysesthesia; MTC=medullary thyroid cancer; TC=thyroid cancer originating in the follicular cells
Source: Elisei 2013;[36] Exelixis 2021 [75]; Schlumberger 2015;[37] Brose 2014;[38] Fleeman 2019[50]

Table 72 EXAM, SELECT and DECISION trials: Most common[a] AEs experienced by patients in the placebo arms

Specific type of AE	MTC		TC			
	EXAM trial		SELECT trial		DECISION trial	
	Placebo n=109		Placebo n=131		Placebo n=209	
	Any-grade, %	Grade ≥3, %	Any-grade, %	Grade ≥3, %	Any-grade, %	Grade ≥3, %
All	93.6	33.0	90.1	29.8	87.6	30.1
Diarrhoea	35.8	1.8	8.4	0	15.3	1.0
Fatigue/asthenia[b]	30.3	2.8	27.5	2.3	25.4	1.4
Nausea	21.1	0	13.7	0.8	11.5	0

[a] Most common defined as any-grade AEs occurring in >20% of patients in any placebo arm
[b] fatigue and asthenia reported separately for EXAM trial, only fatigue data reported in this table
AE=adverse event; MTC=medullary thyroid cancer; TC=thyroid cancer originating in the follicular cells
Source Elisei 2013;[36] Exelixis 2021 [75]; Schlumberger 2015;[37] Brose 2014[38]

8.6 *Appendix 6: EAG revisions to the company RET-mutant MTC model*

EAG revisions	Implementation instructions
R1) Stratified spline 1 knot to extrapolate cabozantinib OS	**Insert sheet named 'EAG Revisions'** In cell C4 enter text "R1" Set value in cell D4=1 In Sheet 'Mechanics' Set value in cell D524 =IF('EAG Revisions'!D4=1,9,7)
R2) Mapped health state utility values using LIBRETTO-001 trial data	In Sheet 'EAG Revisions' In cell C5 enter text "R2" Set value in cell D5 =1 In Sheet 'Country-Specific MTC' Set value in cell E396 =IF('EAG Revisions'!D5=1,0.77,0.8) Set value in cell L396 =0.18 Set value in cell M396 =267 Set value in cell K396 =IF('EAG Revisions'!D5=1,L396/SQRT(M396),(H396-G396)/3.92) Set value in cell E397 =IF('EAG Revisions'!D5=1,0.71,0.5) Set value in cell L397 =0.2 Set value in cell M397 =6 Set value in cell K397 =IF('EAG Revisions'!D5=1,L397/SQRT(M397),(H397-G397)/3.92)
Order parameters in PSA - *Define sampling parameters*	In Sheet 'Variables - MTC' Set value in cell V230=(((1-F230)*F230/'Country-Specific Data MTC'!L396^2)-1)*F230 Set value in cell V231 =(((1-F233)*F233/'Country-Specific Data MTC'!L397^2)-1)*F233 Set value in cell W230 =V230*(1-F230)/F230 Set value in cell W231 =V231*(1-F233)/F233 Set value in cell Y230 =BETA.INV(H230,V230,W230) Set value in cell Y231 =BETA.INV(H233,V231,W231) Set value in cell Z230 =LN(Y230/(1-Y230)) Set value in cell Z231 =LN(Y231/(1-Y231))
- *Generate independent utility value samples*	In Sheet 'Variables - MTC' Name range Y230:Y231 "HSUV_sample_MTC" Name range AI8:AJ8 "sample_MTC_paste" Insert following VBA code (highlighted in italics) into modIndication3_PSA macro: Sheet35.Range("PSA_Range_Ind_3").Value =Sheet35.Range("PSA_Range_Ind_3").Offset(0, -3).Value *[sample_MTC_paste].Offset(iter, 0).Value =Application.WorksheetFunction.Transpose([HSUV_sample_MTC].Value)* myRow =1 Run modIndication3_PSA macro

EAG revisions	Implementation instructions
- *Define difference distribution parameters*	<u>In Sheet 'Variables - MTC'</u> Set value in cell AA230 =AVERAGE(AK9:AK1008)-AVERAGE(AL9:AL1008) Set value in cell AB230 =ABS(VAR(AK9:AK1008)-VAR(AL9:AL1008)) Set value in cell AC230 =AA230^2/AB230 Set value in cell AD230 =AB230/AA230
- *Generate bounded utility value samples*	<u>In Sheet 'Variables - MTC'</u> Name range AP8:AQ8 "Bounded_values_MTC" Name range AE230:AF230 "EAG_values_MTC" Set value in cell AK9 =LN(AI9/(1-AI9)) Set value in cell AL9 =LN(AJ9/(1-AJ9)) Set value in cell AM9 =GAMMA.INV(RAND(),$AC$230,$AD$230) Set value in cell AN9 =IF(VAR($AK$9:$AK$1008)>VAR($AL$9:$AL$1008),AO9+AM9,AK9) Set value in cell AO9 =IF(VAR($AK$9:$AK$1008)>VAR($AL$9:$AL$1008),AL9,AN9-AM9) Set value in cell AP9 =EXP(AN9)/(1+EXP(AN9)) Set value in cell AQ9 =EXP(AO9)/(1+EXP(AO9)) Copy formula in range AK9:AQ9 and paste to range AK9:AQ1009 Add additional line of VBA code to modIndication3_PSA macro: *[sample_MTC_paste].Offset(iter, 0).Value =Application.WorksheetFunction.Transpose([HSUV_sample_MTC].Value)* *[EAG_values_MTC].Value =[Bounded_values_MTC].Offset(iter, 0).Value* Set value in cell L230 =IF('EAG Revisions'!D$5=1,AE$230,IF(ISERROR(BETAINV(H230,J230,K230)),F230,BETAINV(H230,J230,K230))) Copy formula and paste to range L230:L232 Set value in cell L233 =IF('EAG Revisions'!D$5=1,AF230,IF(ISERROR(BETAINV(H233,J233,K233)),F233,BETAINV(H233,J233,K233))) Run modIndication3_PSA macro
R3) Pessimistic selpercatinib OS extrapolation: clinicians' lower plausible limit & R4) Optimistic selpercatinib OS extrapolation: clinicians' upper plausible limit	<u>In Sheet 'EAG Revisions'</u> In cell C6 enter text "R3" Set value in cell D6 =1 In cell C7 enter text "R4" Set value in cell D7 =1 (D6 must =0) <u>In Sheet 'Survival – MTC'</u> =IF('EAG Revisions'!D6=1,3.5,IF('EAG Revisions'!D7=1,1.5,2))

EAG revisions	Implementation instructions
Remove OS from PSA	In Sheet 'EAG Revisions' Set value in cell D9=1 In Sheet 'MTC S(t)' Set value in cell BM17 =IF('EAG Revisions'!D$9=1,BO17,IF(PSA_Toggle_Ind_3=1,BO17,BP17)) Copy formula in cell BM17 and paste to range BM17:BM31 Set value in cell BM53 =IF('EAG Revisions'!D$9=1,BO53,IF(PSA_Toggle_Ind_3=1,BO53,BP53)) Copy formula in cell BM53 and paste to range BM53:BM67 Set value in cell BM125 =IF('EAG Revisions'!D$9=1,BO125,IF(PSA_Toggle_Ind_3=1,BO125,BP125)) Copy formula in cell BM125 and paste to range BM125:BM139

EAG=External Assessment Group; OS=overall survival; PSA=probabilistic sensitivity analysis

8.7 *Appendix 7: EAG revisions to the company RET fusion-positive TC model*

EAG revisions	Implementation instructions
R1) Mapped health state utility values using LIBRETTO-001 trial data	In Sheet 'EAG Revisions' In cell H4 enter text "R1" Set value in cell I4 =1 In Sheet 'Country-Specific Data TC' Set value in cell E384 =IF('EAG Revisions'!I4=1,0.77,0.8) Set value in cell L384 =0.18 Set value in cell M384 =267 Set value in cell K384=IF('EAG Revisions'!I4=1,L384/SQRT(M384),(H397-G397)/3.92) Set value in cell E385=IF('EAG Revisions'!I4=1,0.71,0.5) Set value in cell L385 =0.2 Set value in cell M385 =6 Set value in cell K385 =IF('EAG Revisions'!I4=1,L385/SQRT(M385),(H397-G397)/3.92)
Order parameters in PSA - *Define sampling parameters*	In Sheet 'Variables – TC' Set value in cell V267 =(((1-F267)*F267/'Country-Specific Data TC'!L384^2)-1)*F267 Set value in cell V268 =(((1-F271)*F271/'Country-Specific Data TC'!L385^2)-1)*F271 Set value in cell W267 =V267*(1-F267)/F267 Set value in cell W268 =V268*(1-F271)/F271 Set value in cell Y267 =BETA.INV(H267,V267,W267) Set value in cell Y268 =BETA.INV(H271,V268,W268) Set value in cell Z267 =LN(Y267/(1-Y267)) Set value in cell Z268 =LN(Y268/(1-Y268))
- *Generate independent utility value samples*	In Sheet 'Variables – TC' Name range Y267:Y268 "HSUV_sample_TC" Name range AJ7:AK7 "sample_TC_paste" Insert following VBA code (highlighted in italics) into modIndication4_PSA macro: Sheet36.Range("PSA_Range_Ind_4").Value =Sheet36.Range("PSA_Range_Ind_4").Offset(0, -3).Value *[sample_TC_paste].Offset(iter, 0).Value =Application.WorksheetFunction.Transpose([HSUV_sample_TC].Value)* myRow =1 Run modIndication4_PSA macro

EAG revisions	Implementation instructions
- *Define difference distribution parameters*	<u>In Sheet 'Variables – TC'</u> Set value in cell AA267 =AVERAGE(AL8:AL1007)-AVERAGE(AM8:AM1007) Set value in cell AB267 =ABS(VAR(AL8:AL1007)-VAR(AM8:AM1007)) Set value in cell AE267 =AA267^2/AB267 Set value in cell AF267 =AB267/AA267
- *Generate bounded utility value samples*	<u>In Sheet 'Variables – TC'</u> Name range AQ7:AR7 "Bounded_values_TC" Name range AG267:AH267 "EAG_values_TC" Set value in cell AL8 =LN(AJ8/(1-AJ8)) Set value in cell AM8 =LN(AK8/(1-AK8)) Set value in cell AN8 =GAMMA.INV(RAND(),$AE$267,$AF$267) Set value in cell AO8 =IF(VAR($AL$8:$AL$1007)>VAR($AM$8:$AM$1007),AP8+AN8,AL8) Set value in cell AP8 =IF(VAR($AL$8:$AL$1007)>VAR($AM$8:$AM$1007),AM8,AO8-AN8) Set value in cell AQ8 =EXP(AO8)/(1+EXP(AO8)) Set value in cell AR8 =EXP(AP8)/(1+EXP(AP8)) Copy formula in range AL8:AR8 and paste to range AL8:AR1008 Add additional line of VBA code to modIndication4_PSA macro: *[sample_TC_paste].Offset(iter, 0).Value =Application.WorksheetFunction.Transpose([HSUV_sample_TC].Value)* *[EAG_values_TC].Value =[Bounded_values_TC].Offset(iter, 0).Value* Set value in cell L267 =IF('EAG Revisions'!I$4=1,AG$267,IF(ISERROR(BETAINV(H267,J267,K267)),F267,BETAINV(H267,J267,K267))) Copy formula in cell L267 to range L267:L269 Set value in cell L270 =IF('EAG Revisions'!I$4=1,AH$267,IF(ISERROR(BETAINV(H271,J271,K271)),F271,BETAINV(H271,J271,K271))) Run modIndication4_PSA macro
R2) Pessimistic selpercatinib OS extrapolation: clinicians' lower plausible limit & R3) Optimistic selpercatinib OS extrapolation: clinicians' upper plausible limit	<u>In Sheet 'EAG Revisions'</u> In cell H5 enter text "R2" Set value in cell I5 =1 In cell H6 enter text "R3" Set value in cell I6 =1 (I5 must =0) <u>In sheet 'Survival -TC'</u> Set value in cell D60 =IF('EAG Revisions'!I10=1,18,60) Set value in cell D62 =IF('EAG Revisions'!I10=1,1.5,IF('EAG Revisions'!I11=1,0.9,1.2))

EAG revisions	Implementation instructions
Remove OS from PSA	In Sheet 'EAG Revisions' Set value in cell I9 =1 In Sheet 'TC S(t) (2)' Set value in cell CS857 =IF('EAG Revisions'!I$9=1,CT857,IF(PSA_Toggle_Ind_4=1,CT857,CU857)) Copy formula in cell CS857 and paste to range CS857:CS860 Set value in cell CS868 =IF('EAG Revisions'!I$9=1,CT868,IF(PSA_Toggle_Ind_4=1,CT868,CU868)) Copy formula in cell CS868 and paste to range CS868:CS871

EAG=External Assessment Group; OS=overall survival; PSA=probabilistic sensitivity analysis

Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 Wednesday 24 January 2024** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Mean age used to inform severity modifier calculations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18, Section 1.6 of the EAG report states: "The company used the incorrect age (55 years) in the severity modifier calculation tool. The mean age of the LIBRETTO-001 trial RET-mutant MTC population is **** years and as the severity modifier tool only accepts integers, a value of ** years should have been used." Page 118, Section 6.6 of the EAG report states: "The company calculated expected general population QALYs using an age value of 55 years; however, the mean age of the any-line LIBRETTO-001 trial RET-mutant MTC population was **** years. The severity modifier tool developed by ScHaRR only allows the input of integer age values. When an age value of ** years is used it is inappropriate to use a severity modifier for the comparison of selpercatinib	Please can the text stating that an age of ** years should be used in the severity modifier calculations be removed.	As the efficacy data informing the comparison in the *RET*-mutant MTC population are from the adjusted any-line *RET*-mutant MTC, it would be most appropriate for the age informing the severity modifier calculations to be sourced from the same population. As presented in Table 39, Section B.2.9.1, the mean age in the LIBRETTO-001 any-line *RET*-mutant MTC population after matching is **** years. In addition, the proportion female from the LIBRETTO-001 any-line *RET*-mutant MTC population after matching should be used (****%).	Thank you for clarifying. The EAG agrees with the company that it is more appropriate to use the adjusted age (** years) and sex (****%) values from the MAIC in the severity modifier calculations. Therefore the text has been removed as suggested. However, the values used in and the company clarification model are: starting age=**** years and proportion female=**% (CS, Table 93), which do not correspond to the any-line after matching baseline characteristics. Changing the baseline starting age and proportion female to the any-line after matching baseline characteristics has a negligible effect on the company base case deterministic cost effectiveness results. However, it means that when

versus cabozantinib using company base case probabilistic mean QALY value for patients treated with cabozantinib."			estimating company base case deterministic and probabilistic results for the comparison of selpercatinib versus cabozantinib it is appropriate to apply a severity modifier (x1.2).

Issue 2 Changes in selpercatinib marketing authorisation timelines

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 2, Page 26, Section 24 of the EAG report states that MHRA marketing authorisation application for the RET fusion-positive TC systemic therapy-naïve population was submitted in **********. The footnotes of Table 2 also state: "[a] A positive opinion from the CHMP (**********) has not yet been published. [b] MHRA approval under a conditional marketing authorisation is expected in **********."	Please can the anticipated date of MHRA marketing authorisation application for the RET fusion-positive TC systemic therapy-naïve population be updated to **********. Please can this footnote be updated to the following: "[a] A positive opinion from the CHMP (**********) has not yet been published. [b] MHRA approval under a conditional marketing authorisation is expected in *********."	Since submission, the anticipated timelines for the marketing authorisation of selpercatinib in the RET fusion-positive TC systemic therapy-naïve population have changed. The most recent anticipated timelines have been provided.	This information was not available at the time the EAG report was submitted to NICE. However, the EAG report text has been changed to include the updated information.

Issue 3 Number of patients receiving cabozantinib and vandetanib in LIBRETTO-531

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 27, Section 2.5 of the EAG report states: "The exact number of patients who received cabozantinib and vandetanib is unclear (reported to be n=71 and n=27, respectively, in the subgroup efficacy analyses, n=73 and n=25 in the CONSORT diagram and n=72 and n=25 in the safety population)" Page 43, Section 3.3.2 of the EAG report states: "The exact number of patients who received cabozantinib and vandetanib is unclear (reported to be n=71 and n=27, respectively, in the subgroup efficacy analyses but n=73 and n=25 in the CONSORT diagram and n=72 and n=25 in the safety population)."	Please can the wording stating that the number of patients receiving cabozantinib and vandetanib in the LIBRETTO-531 trial is unclear be removed.	Patient numbers in the cabozantinib and vandetanib treatment arms of the LIBRETTO-531 trial are reported in the Hadoux *et al.* 2023 publication.[1] In the LIBRETTO-531 trial, 73 and 25 patients were randomised to receive cabozantinib and vandetanib, respectively. This comprises the intention-to-treat population. Following randomisation, 71 and 27 patients *received* cabozantinib and vandetanib, respectively. Some patients received a different MKI than they were randomised to due to supply issues, as reported in the publication. Therefore, the difference between the intention-to-treat population and the forest plot displaying subgroup analyses is that the forest plot reports results based on the treatments received. Finally, the safety population included 72 and 25 patients who	Thank you for clarifying. The EAG is unclear how vandetanib supply issues have resulted in more patients receiving vandetanib than were randomised to receive vandetanib. Can the company provide further explanation? Text amended as follows: ***EAR, Table 3, Footnote d*** In the LIBRETTO-531 trial, 73 patients and 25 patients were randomised to receive cabozantinib and vandetanib, respectively (ITT population). However, due to supply issues, the actual number of patients who received cabozantinib and vandetanib was n=71 and n=27, respectively (subgroup efficacy analyses populations). ***EAR, Section 3.3.2***

		received cabozantinib and vandetanib, respectively. The safety population was defined as all patients who underwent randomisation and received at least one dose of trial treatment, as stated in Hadoux *et al.* 2023.	The number of patients randomised to cabozantinib and vandetanib was n=71 and n=27, respectively (intention-to-treat [ITT] population). However, due to supply issues, the actual number of patients who received cabozantinib and vandetanib was n=71 and n=27, respectively (subgroup efficacy analyses populations).

Issue 4 Availability of RET M918T mutation status data for the any-line *RET*-mutant MTC LIBRETTO-001 analysis set

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 69, Section 3.10.4 of the EAG report states: "It is not clear how the company was able to balance RET M918T mutation status between the trials as RET M918T mutation status data were unavailable for the LIBRETTO-001 trial any-line RET-mutant MTC population (CS, Table 13 footnote)." Page 71, Section 3.10.6 of the	Please can these sentences stating that RET M918T mutation status data were unavailable for the LIBRETTO-001 any-line RET-mutant MTC population be removed.	It is incorrect to state that RET M918T mutation status data were unavailable for the LIBRETTO-001 any-line RET-mutant MTC population. As presented in Document B, Section B.2.9.1, Table 39, data on RET M918T mutation status are available for the any-line RET-mutant MTC analysis set from LIBRETTO-001; [redacted]% of the any-line RET-mutant MTC population from LIBRETTO-001 were RET M918T mutant	Thank you for clarifying. The text regarding RET M918T mutation status data has been removed.

EAG report states: "The company states that RET M918T mutation status was adjusted for in the MAICs; however, RET M918T mutation status was not available for patients in the LIBRETTO-001 any-line RET-mutant MTC population (CS, Table 13 footnote)."		positive. The footnote of Table 13 of Document B, Section explains that *complete* data on RET alteration status were unavailable in the clinical study report (CSR) for the any-line RET-mutant MTC analysis set from LIBRETTO-001.	

Issue 5 Testing of the proportional hazards assumption in the RET fusion-positive TC population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 81, Section 3.11.6 of the EAG report states: "The company did not test any of the data used in the unadjusted indirect comparisons to determine whether the PH assumption held".	Please can this sentence be removed from the EAG report.	It is incorrect to state that the proportional hazards (PH) assumption was not tested for the data informing the ITCs in the TC population. The PH assumption was tested for selpercatinib versus all comparators presented in the submission. The results of the tests for the PH assumption are presented in Appendix O.2 of the CS, which present log-cumulative hazard plots, Schoenfeld residual plots and global p-values for selpercatinib versus the relevant comparators. It was not possible to generate Schoenfeld residual	The text on p81 has been replaced with the following: ***EAR, Section 3.10.6*** As Cox PH models were used to estimate HRs and 95% CIs, the company assessed the validity of the PH assumption for each unadjusted indirect comparison (CS, Appendix O). The company considered log-cumulative hazard plots, Schoenfeld residual plots and the global Schoenfeld residuals test of proportional hazards, and concluded that,

		plots for selpercatinib versus lenvatinib or sorafenib, however the associated p-values are calculated independently and are reported in Appendix O.2.	for selpercatinib versus BSC (SELECT trial placebo arm data), the PH assumption appears to be violated for both OS and PFS. The EAG agrees with this conclusion. The EAG also considers that the PH assumption appears to be violated for the comparison of selpercatinib versus sorafenib OS data. Therefore, the reported HRs for selpercatinib versus BSC (SELECT trial placebo arm PFS and OS data) and for selpercatinib versus sorafenib (OS data) may not provide accurate numerical estimates of comparative efficacy.

Issue 6 Company methodology for selection of base case extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93, Section 4.7.1 of the EAG report states: "Company model selection involved consideration of statistical fit, visual inspection of the observed OS K-M curves and the clinical plausibility of	Please can this be amended as follows: "Company model selection involved consideration of statistical fit, visual inspection of the observed OS K-M curves, the clinical plausibility of extrapolations (based on clinical expert estimates of long-term survival) **and NICE Committee**	As outlined in Document B, Section B.3.3, extrapolation selection also considered the preferences of the NICE Committee during the prior appraisal of selpercatinib as a treatment for advanced RET-altered thyroid cancer following	The EAG report has been updated to include the additional detail requested by the company.

extrapolations (based on clinical expert estimates of long-term survival)." "The company considered that the stratified Weibull model provided the most clinically plausible estimates of long-term survival for patients treated with selpercatinib and BSC; therefore, this distribution was used in the company base case." Page 93, Section 4.7.1 of the EAG report states: "The company considered that the (unstratified) loglogistic distribution provided the most accurate long-term PFS estimates for patients treated with selpercatinib, cabozantinib and BSC when compared to clinician estimates; therefore, this distribution was used in the company base case analysis." Page 94, Section 4.7.2 of the EAG report states: "The company considered that the piecewise exponential distribution provided the most accurate long-term OS estimates for patients treated	**preferences during TA742 (based on an earlier data cut of the same analysis sets of LIBRETTO-001)**." "The company considered that the stratified Weibull model provided the most clinically plausible estimates of long-term survival for patients treated with selpercatinib and BSC**, and aligned with Committee preferences in TA742**; therefore, this distribution was used in the company base case." "The company considered that the (unstratified) loglogistic distribution provided the most accurate long-term PFS estimates for patients treated with selpercatinib, cabozantinib and BSC when compared to clinician estimates**, and aligned with Committee preferences in TA742**; therefore, this distribution was used in the company base case analysis." "The company considered that the piecewise exponential distribution provided the most accurate long-term OS estimates for patients treated with selpercatinib, lenvatinib and BSC when compared to clinician estimates**, and aligned with Committee preferences in TA742**; this distribution was used in the company base case analysis." "The company considered that, for selpercatinib, lenvatinib and BSC, the stratified Weibull distribution provided the most accurate long-term PFS estimates when compared to clinician estimates**, and**	prior systemic therapy, as this appraisal was based on an earlier data cut of the same analysis sets of LIBRETTO-001 used to inform the efficacy of selpercatinib and BSC in this appraisal. This should be acknowledged where relevant throughout the EAG report.	

with selpercatinib, lenvatinib and BSC when compared to clinician estimates; this distribution was used in the company base case analysis." "The company considered that, for selpercatinib, lenvatinib and BSC, the stratified Weibull distribution provided the most accurate long-term PFS estimates when compared to clinician estimates; this distribution was used in the company base case analysis."	**aligned with Committee preferences in TA742**; this distribution was used in the company base case analysis."		

Issue 7 Utility values derived from EORTC QLQ-C30 data from LIBRETTO-001

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 95 of the EAG report states: "The company considered that EORTC QLQ-C30 data from the LIBRETTO-001 trial produced implausible health state utility values when mapped to EQ-5D data (CS, Table 81)."	Please can this be amended as follows: "The company considered that EORTC QLQ-C30 data from the LIBRETTO-001 trial produced implausible health state utility values when mapped to EQ-5D data (CS, Table 81). **The NICE Committee also concluded that these utility values were implausible during TA742**."	As outlined in Document B, Section B.3.4.2, as part of the previous appraisal of selpercatinib for RET-altered TC and MTC following prior systemic therapy (TA742), the Committee concluded that the utility values produced from the EORTC QLQ-C30 data from the LIBRETTO-001 were implausible. Alongside the Company's conclusion regarding the implausibility of these utility values, the	The utility values presented in CS, Table 81 are from the January 2023 DCO of the LIBRETTO-001 trial and therefore could not have been presented to the NICE AC Committee during TA742. No change required.

		Committee's (and EAG's) agreement during TA742 should be acknowledged.	

Issue 8 Inaccurate presentation of Company clinical expert survival estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout Section 6.2 and Section 6.3, the EAG report presents the "Clinical experts' plausible range" of survival estimates for selpercatinib and cabozantinib. When collecting feedback from clinical experts, Lilly elicited values for the clinicians 'most likely value', 'lower plausible limit' and 'upper plausible limit' for survival at each timepoint. However, the EAG report does not provide any context to these estimates, most notably, it does not explain that when presented for selpercatinib (Table 48, Table 51), these ranges refer to the 'lower plausible limit' and 'upper plausible limit' provided by the clinicians. Moreover, when reporting clinician estimates for cabozantinib OS (Table 49), the	Please can the EAG report be amended to provide some context to the clinical expert estimates provided. Some suggested wording is provided below: "**The Company clinical experts provided three landmark survival estimates: the most likely value, the lower plausible limit and the upper plausible limit. The lower and upper plausible limits were defined as being extremely unlikely that the true value is less than/higher than this value.**" Moreover, the EAG report should be amended to consistently provide the range of 'most plausible value' provided by the clinical expert estimates, alongside the full range of values based on the 'upper plausible limit' and 'lower plausible limit'.	It is inaccurate to present the range of clinical expert estimates from the lower plausible limit to the upper plausible limit without providing an explanation of these values. Based on the definition of these values, the range of clinician estimates provide extreme upper and lower plausible limits of uncertainty for the survival estimates. Furthermore, it is inaccurate to inconsistently report the range of 'most plausible value' and the range of 'upper plausible limit' and 'lower plausible limit'. • When the range of 'most plausible value' is presented for the cabozantinib OS, the Company's base case extrapolation ([redacted] falls [redacted] this range at 10 years (10%–20%); if the range of 'upper	The EAG report text has been amended to include the additional text requested by the company. For consistency, both clincians' plausible range and most likely values have been presented in EAG report, Table 48, Table 49 and Table 51.

EAG report cites the range of 'most likely values' provided by the clinicians.		plausible limit' and 'lower plausible limit' were used (5%–25%), the Company's base case extrapolation falls within this range. • In contrast, when the range of 'upper plausible limit' and 'lower plausible limit' are reported for selpercatinib OS, the EAG's pessimistic OS extrapolation ([redacted]) falls within this range at 10 years (30%–60%); if the range of 'most plausible value' is used (35%–50%), the EAG's pessimistic OS extrapolation falls [redacted] this range.	

Issue 9 Inaccurate description of alignment of EAG's preferred cabozantinib OS estimates to clinical expert estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 110, Section 6.2.1 of the EAG report states: "The EAG considers that applying the HR to the (BSC) stratified spline 1 knot distribution generates estimates that are closer to company clinical expert 10-year and 20-year OS estimates than the	Please can this be amended as follows: "The EAG considers that applying the HR to the (BSC) stratified spline 1 knot distribution generates estimates that are closer to company clinical expert 10-year ~~and 20-year~~ OS estimates than the estimates generated by the (BSC) stratified Weibull distribution chosen by the company (Table 49). **However, applying the HR to the**	It is incorrect to state that that the EAG's preferred approach brings the OS estimates at 20 years closer to the 20-year OS estimates provided by the clinical experts than the Company's base case approach. The 20-year estimate based on the Company's base case is 0.85% and the 20-year estimate based on the	The EAG report text has been amended as follows: ***EAR Section 6.2.1*** "In the company clarification base case analysis, 10-year OS estimates for patients treated with cabozantinib were slightly lower than the most likely values suggested

estimates generated by the (BSC) stratified Weibull distribution chosen by the company (Table 49)."	**(BSC) stratified spline know 1 distribution generates estimates that are further from the company clinical expert 20-year OS estimates than the estimates generated by the (BSC) stratified Weibull distribution chosen by the company.**"	EAG's preferred extrapolation is 2.24%. The range of 'most plausible values' provided by the clinical experts is 0%–2%; the Company's estimate falls within this range, whilst the EAG's estimate falls above this range. As such, it is incorrect to state that the EAG's preferred approach brings the 20-year OS estimates closer to the clinical expert estimates than the Company's base case approach.	by company clinical expert estimates. The EAG considers that applying the HR to the (BSC) stratified spline 1 knot distribution generates a 10-year OS estimate that is closer to the range of most likely values suggested by company clinical experts than the estimate generated by the (BSC) stratified Weibull distribution chosen by the company (Table 49). Applying the HR to the (BSC) stratified spline 1 knot distribution generates a 20-year OS estimate that is slightly above the range of most likely values suggested by company clinical experts than the estimate generated by the (BSC) stratified Weibull distribution."

Issue 10 Insufficient information presented on utility values derived from the RET fusion-positive TC population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report outlines that the EAG's preferred source of utility values are from the RET fusion-positive TC population of	As well as outlining the benefits of sourcing utility values from the RET fusion-positive TC population of LIBRETTO-001, the EAG report should acknowledge the limited	The EAG report presents insufficient information on the utility values derived from the RET fusion-positive TC	The text has been updated with the additional detail requested by the company.

LIBRETTO-011, mapped from EORTC-QLQ-C30 data to EQ-5D. Page 117, Section 6.5 of the EAG report states: "The EAG alternative approach used RET fusion-positive TC population health state utility values mapped (Young 2015[2] algorithm) from EORTC-QLQ-C30 data to EQ-5D data (Table 53). The EAG considers these health state utility values are more appropriate than the Fordham 2015[3] values as they are derived from LIBRETTO-001 trial HRQoL data and more accurately reflect the length of time patients spend in the model progressed disease health state." "Due to the small number of patients informing the progressed disease health state utility value, […]"	patient numbers that these utility values are derived from. For the progression-free health state, the utility values are derived from a total of ** patients (*** assessments) and for the progressed disease health state, the utility values are derived from a total of * patients (* assessments). A suggested amendment is presented below: "The EAG alternative approach used RET fusion-positive TC population health state utility values mapped (Young 2015[2] algorithm) from EORTC-QLQ-C30 data to EQ-5D data (Table 53). The EAG considers these health state utility values are more appropriate than the Fordham 2015[3] values as they are derived from LIBRETTO-001 trial HRQoL data and more accurately reflect the length of time patients spend in the model progressed disease health state. **However, the EAG acknowledge that these utility values are derived from a small number of patients (**** for progression-free; ****for progressed disease).**" "Due to the small number of patients (**********) informing the progressed disease health state utility value, […]"	population of the LIBRETTO-001 trial to understand the advantages and disadvantages of using these utility values. In particular, it is inaccurate to propose that utility values derived from the RET fusion-positive TC population of LIBRETTO-001 are more accurate than alternative sources, without providing additional information on the sample size that these values have been derived from, especially for the progressed disease utility value.	

Minor Clarifications

Issue 11 Minor clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Section 1.4 of the EAG report states: "However, the LIBRETTO-001 trial median follow-up (**** months) is longer than the LIBRETTO-531 trial interim analysis, selpercatinib arm median follow-up (***** months)." Page 34, Section 2.5.3 of the EAG report states: "The EAG acknowledges, however, that the LIBRETTO-531 trial has a substantially shorter follow-up than the LIBRETTO-001 trial (LIBRETTO 531 trial interim analysis, selpercatinib arm median follow-up=***** months; LIBRETTO-001 trial median follow-up=**** months)."	Please can the text be amended as follows: "However, the LIBRETTO-001 trial median follow-up (**PFS median follow-up:** **** months) is longer than the LIBRETTO-531 trial interim analysis, selpercatinib arm median follow-up (***** months)." "The EAG acknowledges, however, that the LIBRETTO-531 trial has a substantially shorter follow-up than the LIBRETTO-001 trial (LIBRETTO 531 trial interim analysis, selpercatinib arm median **PFS** follow-up=***** months; LIBRETTO-001 trial median **PFS** follow-up=**** months)."	When citing median duration of follow-up from LIBRETTO-001 or LIBRETTO-531, the EAG report should state which endpoint is being referred to. The median duration of follow-up data cited in this example are for PFS.	EAG report text has been updated with the additional detail requested by the company.
Page 25, Section 2.3.2 of the EAG report states: "Clinical advice to the	Please can the text be amended to: "Clinical advice to the company is that 90% to 95% of adult patients with radioactive iodine	As per Section B.1, Document B of the CS, during interviews conducted to support this submission, UK clinical experts stated that of	EAG report text amended as follows: ***EAR, Section 2.3.2***

company is that 90% to 95% of adult patients with radioactive iodine therapy-refractory differentiated TC are treated with lenvatinib or sorafenib and that the remaining patients receive BSC; however, sorafenib is rarely used." 	therapy-refractory differentiated TC **that receive MKIs** are treated with lenvatinib, **with** sorafenib rarely used." 	patients treated with MKIs, 90-95% currently receive lenvatinib. This is incorrectly reported in the EAG report. 	Clinical advice to the company is that 90% to 95% of adult patients with radioactive iodine therapy-refractory differentiated TC who receive an MKI are treated with lenvatinib or sorafenib; however, sorafenib is rarely used.
Page 32, Section 2.5.1 of the EAG report states: "For patients with *RET* fusion-positive TC, the population specified in the company decision problem includes children and young adults aged 12 to 18 years, i.e., is broader than the *RET* fusion-positive TC population (adults only) specified in the final scope issued by NICE." 	Please can the text be amended to: "For patients with *RET* fusion-positive TC, the population specified in the company decision problem includes **adolescents** aged 12 to 18 years, i.e., is broader than the *RET* fusion-positive TC population (adults only) specified in the final scope issued by NICE." 	An amendment has been suggested to align with the anticipated MHRA marketing authorisation wording for selpercatinib within this population, as presented in Section B.1.2 of the CS. 	EAG report text amended as suggested.
Page 38, Section 3.2 of the EAG report states: "The EAG agrees that the LIBRETTO-321 trial provides less relevant and less robust evidence than the LIBRETTO-001 trial (due to its location [China], sample size [n=29 for *RET*-mutant MTC and n=1 for *RET* fusion-positive TC] and	Please can the text be amended to: "The EAG agrees that the LIBRETTO-321 trial provides less relevant and less robust evidence than the LIBRETTO-001 trial (due to its location [China], sample size [n=29 for *RET*-mutant MTC and n=1 for *RET* fusion-positive TC] and **ORR** follow-up [8.7 months]**, based on the March 2021 data cut**)." 	When stating the median duration of follow-up, the relevant endpoint and data cut should also be mentioned, per Zheng et al. (2022).[4] 	EAG report text amended as follows: ***EAR, Section 3.2*** The EAG agrees that the LIBRETTO-321 trial provides less relevant and less robust evidence than the LIBRETTO-001 trial (due to its location [China], sample size

follow-up [8.7 months]).”			[n=29 for RET-mutant MTC and n=1 for RET fusion-positive TC] and ORR follow-up [8.7 months] at the March 2021 DCO).
Page 56, Section 3.7.3 of the EAG report states: “LIBRETTO-531 trial data has substantially shorter follow-up than LIBRETTO-001 trial data (approximately ** months for DoR and approximately ** months for PFS and OS).”	Please can this be amended as follows: “LIBRETTO-531 trial data has substantially shorter follow-up than LIBRETTO-001 trial data (**median duration of follow-up in the cabozantinib/vandetanib-naïve RET-mutant MTC population is approximately 39 months for DoR, 42 months for PFS and ** months for OS**).”	When citing median duration of follow-up, the EAG report should state which trial and analysis set is being referred to. It is currently unclear whether the median duration of follow-up for DoR, PFS and OS cited by the EAG is from LIBRETTO-001 or LIBRETTO-531. As Section 3.7.3 of the EAG report discusses the RET-mutant MTC population, median duration of follow-up in the cabozantinib/vandetanib-naïve RET-mutant MTC analysis set of LIBRETTO-001 should be cited.	EAG report text amended as follows: ***EAR, Section 3.7.3:*** (LIBRETTO-001 trial cabozantinib/vandetanib-naïve *RET*-mutant MTC population median DoR follow-up: 39 months; PFS follow-up: 42 months; median OS follow-up: ** months)
Page 64, Section 3.10 of the EAG report states: “The company considered (CS, p102) that although the LIBRETTO-531 trial investigates the efficacy of selpercatinib versus cabozantinib or vandetanib, the LIBRETTO-531 trial[5] data	Please may this statement be amended as follows: “The company considered (CS, p102) that although the LIBRETTO-531 trial investigates the efficacy of selpercatinib versus cabozantinib or vandetanib, the LIBRETTO-531 trial[5] data follow-up is too short to inform a useful **long-term cost-effectiveness** analysis.”	The LIBRETTO-531 trial provides convincing and high-quality comparative efficacy data for selpercatinib versus cabozantinib, in the short term. This trial was not used in the cost-effectiveness analysis informing the submission as these data are considered too immature, and	EAG report text amended as follows: ***EAR, Section 3.10:*** The company considered (CS, p102) that although the LIBRETTO-531 trial investigates the efficacy of selpercatinib versus cabozantinib or

follow-up is too short to inform a useful comparative efficacy analysis."		therefore OS and PFS extrapolations included in the cost-effectiveness model would be associated with considerable uncertainty. This is outlined throughout Document B of the CS.	vandetanib, the LIBRETTO-531 trial[5] data follow-up is too short to inform a useful comparative (efficacy or cost effectiveness) analysis.
Page 108, Section 6.1.1 of the EAG report states: "however, the EAG considers the data are currently of limited value for informing the economic model as follow-up is short (median interim follow up in the selpercatinib arm of 12.45 months compared to 42.4 months in the LIBRETTO-001 trial)."	Please can the text be amended as follows: "however, the EAG considers the data are currently of limited value for informing the economic model as follow-up is short (median interim follow up for **PFS** in the selpercatinib arm of [redacted] months compared to [redacted] months in the LIBRETTO-001 trial)."	When stating the median duration of follow-up, the relevant endpoint should be stated. In this example, the median duration of follow-up for PFS is reported.	EAG report text has been amended as follows: ***EAR, Section 6.1.1*** …(median interim PFS follow up in the selpercatinib arm of [redacted] months compared to [redacted] months in the LIBRETTO-001 trial).

Typographical Errors

Issue 12 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 34, Section 2.5.3 of the EAG report states: "The company considered that the EXAM trial placebo arm PFS and OS data could be used as proxies for BSC data; clinical	Please can the text be amended to: "The company considered that the EXAM trial placebo arm PFS and OS data could be used as proxies for BSC data; clinical advice to the EAG is that this was reasonable for PFS but not	Typographical error. The value stated is incorrect; in the EXAM trial, 49.5% (55/111) of placebo arm patients received subsequent	Thank you for highlighting. Text updated as suggested.

advice to the EAG is that this was reasonable for PFS but not for OS as, in the EXAM trial, 45.9% of placebo arm patients subsequently received systemic therapies." Page 65, Section 3.10.1 of the EAG report states: "clinical advice to the EAG is that this assumption is reasonable for PFS but not for OS as, in the EXAM trial, 45.9% of placebo arm patients subsequently received systemic therapies."	for OS as, in the EXAM trial, **49.5**% of placebo arm patients subsequently received systemic therapies." "clinical advice to the EAG is that this assumption is reasonable for PFS but not for OS as, in the EXAM trial, **49.5**% of placebo arm patients subsequently received systemic therapies."	systemic therapies, as reported in Schlumberger *et al.* (2017).	
Page 41, Section 3.3.1 of the EAG report states: "Additional data, from earlier DCOs (16 December 2019 and 17 June 2021) are provided in CS, Appendix N.3."	Please can the text be amended to: "Additional data, from earlier DCOs (16 December 2019 and **15** June 2021) are provided in CS, Appendix N.3."	Typographical error. As stated on Page 61, Section B.2.4 of the CS, a prior DCO from LIBRETTO-001 occurred on 15th June 2021, rather than 17th June 2021.	Thank you for highlighting. Text updated as suggested.
Page 46, Section 3.4 of the EAG report states: "a higher proportion of any-line patients had ECOG PS≥1 (56.6%), compared with cabozantinib/vandetanib-naïve patients (47.6%)"	Please can the text be amended to: "a higher proportion of any-line patients had ECOG PS≥1 (**62.4**%), compared with cabozantinib/vandetanib-naïve patients (**51.7**%)"	Typographical error. The values presented in the EAG report refer to patients with ECOG PS of 1, rather than ECOG PS of 1 or more. Values for patients with ECOG PS of 1 or more are presented in Table 7, Page 49, Section B.2.3.2 of the CS. Alternatively, please can the text be updated to state that the reported values are for patients with ECOG PS=1.	Thank you for highlighting this. Text amended as suggested.

Table 13, Page 55, Section 3.7.2 of the EAG report states: Patients who progressed or died, n (%) | [redacted] | [redacted]	Please can this be amended to: Patients who progressed or died, n (%) | [redacted] | [redacted]	Typographical error. The number (and proportion) of cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC who progressed or died according to investigator assessment in the LIBRETTO-001 trial reported is incorrect. The correct data are reported in Table 70, Page 146, Appendix N1.1 of the CS Appendices.	Thank you for highlighting this. Text amended as suggested.
Table 13, Page 55, Section 3.7.2 of the EAG report includes a footnote stating: "Source: CS, Table 20 to Table 23, CS Appendix N1.1, p143, Table 68 and Table 69, Clarification Question A10 and Clarification Question A11"	Please can this footnote be amended to: "Source: CS, Table 20 to Table 23, CS Appendix N1.1, p143, Table 68**,** Table 69 **and Table 70**, Clarification Question A10 and Clarification Question A11"	Typographical error. The data presented in Table 13 of the EAG report also includes data from Table 70, Page 143, Appendix N1.1 of the CS.	Thank you for highlighting this. Text amended as follows: ***EAR, Table 13, Legend:*** Source: CS, Table 20 to Table 23, CS Appendix N1.1, p143, Table 68 to Table 70…
Page 56, Section 3.7.3 of the EAG report states: "LIBRETTO-531 trial interim efficacy analyses (May 2023 DCO) are reported in the CS (Section B.2.6.3 and Appendix M) median follow-up was 12 months."	Please can this be amended to: "LIBRETTO-531 trial interim efficacy analyses (May 2023 DCO) are reported in the CS (Section B.2.6.3 and Appendix M) median **PFS** follow-up was [redacted] months."	For consistency with the CS, please may the median PFS follow-up be reported to 2 decimal points, as per Page 93, Section B.2.6.3 of the CS. Furthermore, it should be clarified that the median	Thank you for highlighting this. Text amended as suggested. For consistency, the EAG has changed the

<table>
<tr><td></td><td></td><td>duration of follow-up reported is for PFS. Finally, as these data are not published, please can these data be marked as confidential.</td><td>value for LIBRETTO-531 trial median PFS follow-up throughout the EAR to [redacted] months.</td></tr>
<tr><td>Table 14, Page 57, Section 3.7.3 of the EAG report states:
<table><tr><th>Median duration of follow-up</th><th>Selpercatinib
(n=193)</th><th>Physician's choice
(n=97)</th></tr></table></td><td>Please can this be amended to:
<table><tr><th>Median duration of follow-up</th><th>Selpercatinib
(n=193)</th><th>Physician's choice
(n=98)</th></tr></table></td><td>Typographical error.
The number of patients in the physician's choice arm of LIBRETTO-531 for the efficacy analyses is 98, as per Section B.2.6.3 of Document B of the CS.</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
<tr><td>Table 15, Page 57, Section 3.7.3 of the EAG report states:
<table><tr><td>Median DoR, months (range)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Please can this be amended to:
<table><tr><td>Median OS, months (95% CI)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Typographical error.
These data are median DoR and associated 95% CIs, rather than the range.</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
<tr><td>Table 15, Page 57, Section 3.7.3 of the EAG report states:
<table><tr><td>Median PFS, months (range)</td><td>NE (NE to NE)</td><td>NE (29.77 to NE)</td></tr></table></td><td>Please can this be amended to:
<table><tr><td>Median PFS, months (95% CI)</td><td>NE (NE to NE)</td><td>16.8 (12.2 to 25.1)</td></tr></table></td><td>Typographical error.
These data are median PFS and associated 95% CIs, rather than the range.</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
<tr><td>Table 15, Page 57, Section 3.7.3 of the EAG report states:
<table><tr><td>Median OS, months (range)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Please can this be amended to:
<table><tr><td>Median OS, months (95% CI)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Typographical error.
These data are median OS and associated 95% CIs, rather than the range.</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Furthermore, these data are not yet published so should be marked as confidential. These are not currently marked as confidential in the EAG report, so please can confidentiality highlighting be added.</td><td></td></tr>
<tr><td>Table 15, Page 57, Section 3.7.3 of the EAG report states:
<table><tr><td>OS rate ≥12 months (95% CI)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>OS rate ≥24 months (95% CI)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Please can this be amended to:
<table><tr><td>OS rate ≥12 months (95% CI)</td><td>**********</td><td>**********</td></tr><tr><td>OS rate ≥24 months (95% CI)</td><td>**********</td><td>**********</td></tr></table></td><td>Typographical error.
Data for PFS rate ≥12 months and ≥24 months has been reported here instead of data for OS rate ≥12 months and ≥24 months. PFS rate data are reported in Table 32, Page 94 of the CS.
Furthermore, these data are not yet published, so should be marked as confidential.</td><td>Company are correct that the EAG reports the effect sizes for PRF instead of OS</td></tr>
<tr><td>Table 16, Page 58, Section 3.7.3 of the EAG report states:
<table><tr><th>Outcome</th><th>Selpercatinib (n=193)</th><th>Cabozantinib (n=71)</th></tr></table></td><td>Please can this be amended to:
<table><tr><th>Outcome</th><th>Selpercatinib (n=129)</th><th>Cabozantinib (n=71)</th></tr></table></td><td>Typographical error.
The correct number of patients in the selpercatinib arm is 129, as reported in Hadoux et al. (2023).</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
<tr><td>Table 18, Page 60, Section 3.7.4 of the EAG report states that median investigator-assessed DoR (range) in the RET fusion-positive TC systemic therapy-naïve population is “NE (48.9 to NE)</td><td>Please can this be amended to state that median DoR (95% CIs) are reported with the following value: “**********”.</td><td>Typographical error.
The correct values for median DoR and associated 95% CIs are reported in Table 71, Appendix N.1.2 of the CS.</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
</table>

Page 63, Section 3.8.3 of the EAG report states: "Data were available for **/24 (****%) systemic therapy-naïve patients with RET fusion-positive TC."	Please can this be amended as follows: "Data were available for **/24 (****%) systemic therapy-naïve patients with RET fusion-positive TC."	Typographical error.	Thank you for highlighting this. Text amended as suggested.
Page 63, Section 3.9 of the EAG report states: "For patients with RET fusion-positive TC, there is no direct comparative evidence and few patients (n=66) have been treated with selpercatinib; of the treated patients, most (42/66, 63.6%) were not systemic therapy-naïve patients."	Please can this be amended as follows: "For patients with RET fusion-positive TC, there is no direct comparative **safety** evidence and few patients (**RET fusion-positive TC safety analysis set:** n=66) have been treated with selpercatinib; of the treated patients, most (**41**/66, **62.1**%) were not systemic therapy-naïve patients."	Typographical error. The correct number of patients in the RET fusion-positive TC safety analysis set that had receive prior systemic therapy is reported in Figure 9, Section B.2.3.4 of Document B of the CS.	Thank you for highlighting this. Text amended as suggested.
Page 81, Section 3.11.6 of the EAG report states: "However, the LIBRETTO-001 trial systemic therapy-naïve RET fusion-positive TC population was very small (n=22)"	Please can this be amended as follows: "However, the LIBRETTO-001 trial systemic therapy-naïve RET fusion-positive TC population was very small (n=**24**)"	Typographical error.	Thank you for highlighting this. Text amended as suggested.
Table 35, Page 97, Section 4.8.1 of the EAG report presents adverse event utility decrements and durations used for patients with *RET*-mutant MTC and *RET* fusion-positive TC.	Please can utility decrements and durations for the following adverse events for patients with *RET* fusion-positive TC be removed from the table: • Muscosal inflammation • Vomiting • Dehydration • Weight increased • Ascites	These adverse events were not included for the *RET* fusion-positive TC patient population in Table 83 of the Company submission, and therefore, were not included in the model.	Thank you for highlighting this. Text amended as suggested.

<table>
<tr><td></td><td>Sepsis
Hyperkalaemia
Hypophosphatemia
Hyperglycaemia
Hypercalcemia</td><td></td><td></td></tr>
<tr><td>Table 41, Page 102, Section 4.9.3 of the EAG report states:
<table><tr><td>Dehydration</td><td>£500.0 (assumption)0</td></tr></table></td><td>Please may the table be amended as follows:
<table><tr><td>Dehydration</td><td>£500.0 (assumption)~~0~~</td></tr></table></td><td>Typographical error.</td><td>Thank you for highlighting this. Text amended as suggested.</td></tr>
<tr><td>Table 48, Page 111, Section 6.2.1 of the EAG report states:
<table><tr><td>Revised company base case (adjustment factor of 2): stratified Weibull</td><td>******</td><td>******</td></tr></table></td><td>Please may the table be amended as follows:
<table><tr><td>Revised company base case (adjustment factor of 2): stratified Weibull</td><td>******</td><td>******</td></tr></table></td><td>Typographical error.
The 10-year and 20-year survival estimates reported for the revised company base case are incorrect. The correct values are reported in Table 16 of the Clarification Questions Response.</td><td>The values reported in Table 51 of the EAG report correspond to the selpercatinib survival estimates in the company clarification model at 10.011 years (‘PSM!Y557’) and 20.003 years (‘PSM!Y1078’). The values in Table 16 of the company clarification response appear to represent</td></tr>
</table>

			survival estimates at slightly earlier timepoints of 9.973 years ('PSM!Y555') and 19.984 years ('PSM!Y1077'). Therefore, no change is required.
Table 51, Page 114, Section 6.2.2 of the EAG report states: Revised company base case: piecewise exponential with adjustment factor of 1.2 | [redacted] | [redacted]	Please may the table be amended as follows: Revised company base case: piecewise exponential with adjustment factor of 1.2 | [redacted] | [redacted]	Typographical error. The 10-year and 20-year survival estimates reported for the revised company base case are incorrect. The correct values are reported in Table 17 of the Clarification Questions Response.	The values reported in EAG report Table 51 correspond to the selpercatinib survival estimates in the company clarification model at 10.011 years ('PSM!Y557') and 20.003 years ('PSM!Y1078'). The values in Table 17 of the company clarification response appear to represent survival estimates at

<table>
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<td></td>
<td>slightly earlier timepoints of 9.973 years (‘PSM!Y555’) and 19.984 years (‘PSM!Y1077’). Therefore, no change is required.</td>
</tr>
<tr>
<td>Table 53, Page 118, Section 6.5 of the EAG report presents health state utility values used in the company model:
<table><tr><td>Progression-free</td><td>0.80 (0.02)</td><td rowspan="2">Fordham 2015</td><td>**********</td></tr><tr><td>Progressed disease</td><td>0.50 (0.03)</td><td>**********</td></tr></table></td>
<td>Please may the table be amended as follows:
<table><tr><td>Progression-free</td><td>0.80 (0.02)</td><td rowspan="2">Fordham 2015</td><td>******** ****</td></tr><tr><td>Progressed disease</td><td>0.50 (0.03)</td><td>******** ****</td></tr></table>
Furthermore, please may it be clarified that standard deviation values are presented for the Company base case utility values.</td>
<td>Typographical error.

The standard errors of the utility values derived from the RET fusion-positive TC population of LIBRETTO-001 are incorrect. The correct values are reported in Table 81, page 177, Document B of the CS.

Furthermore, the values in brackets are incorrectly described as standard errors; these are standard deviation values.</td>
<td>The bracketed values in Table 53 of the EAR are intended to be standard errors, as the EAG considers that standard errors are more informative than standard deviations. The bracketed values for the Fordham utility values correspond to the standard errors used in the company model. Clarification has been added to the table footnote that standard errors have been</td>
</tr>
</table>

			sourced from the company model.
Table 64, Page 128, Section 6.7.2 of the EAG report includes a footnote stating: "Source: Table 24 of the clarification question response".	Please may this footnote be amended as follows: "Source: **Table 30** of the clarification question response".	Typographical error. The corresponding table for the base case probabilistic results (*RET* fusion-positive TC) is Table 30 in the Company clarification response.	Thank you for highlighting this. Text amended as suggested.
Table 66, Page 135, Section 8.1.2 of the EAG report includes a footnote stating: "[c] Cabozantinib (n=73) or vandetanib (n=25)"	Please can this footnote be removed.	Typographical error. This footnote is out of place in the context of this table (it refers to patient numbers from LIBRETTO-531, rather than LIBRETTO-321). Furthermore, there is no superscript 'c' in this table.	Thank you for highlighting this. Text amended as suggested.

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Footnote a, Table 9, Page 47, Section 3.5	The age range of patients included in the RET fusion-positive TC population of LIBRETTO-001 is does not need to be marked as confidential as these data are	Please can the confidentiality highlighting be removed as follows: **"[a] No patients were aged <18 years"**	Thank you for highlighting. Confidentiality marking removed.

<table>
<tr><td></td><td>published. As such, the confidentiality highlighting can be removed.</td><td></td><td></td></tr>
<tr><td>Page 56, Section 3.7.2</td><td>Median DoR, median PFS and median OS not being reached by the RET-mutant MTC any-line population in the LIBRETTO-001 trial should be marked as confidential as these data are not published.</td><td>Please can confidentiality highlighting be added as follows:

“DoR was [redacted] in either population because too few patients who achieved ORR (CR or PR) subsequently progressed and/or died; most patients who achieved an ORR were still responding to treatment at the time of the 13 January 2023 DCO (as shown by the DoR rates in Table 13). Similarly, median PFS and median OS [redacted] in either population.”</td><td>Thank you for highlighting. Confidentiality marking added.</td></tr>
<tr><td>Page 59, Section 3.7.4</td><td>The number of patients included in the RET fusion-positive TC systemic therapy-naïve and any-line populations of the LIBRETTO-001 trial does not need to be marked as confidential as these data are published.</td><td>Please can confidentiality highlighting be amended as follows:

“As reported in the CS (Table 16), some patients in the systemic therapy-naïve and any-line populations received selpercatinib beyond progression: [redacted]24 [redacted] and [redacted]/65 [redacted], respectively.”</td><td>Thank you for highlighting. Confidentiality marking removed.</td></tr>
<tr><td>Table 18, Page 60, Section 3.7.4</td><td>Median PFS and PFS rate at ≥12 and ≥24 months does not need to be marked as confidential as these data are published in Wirth et al. (2023).[6]</td><td>Please can the confidentiality highlighting be removed as follows:

<table><tr><td>Median PFS, months (range)</td><td>NE (44.2 to NE)</td></tr><tr><td>PFS rate ≥12 months (95% CI)</td><td>95.2 (70.7 to 99.3)</td></tr><tr><td>PFS rate ≥24 months (95% CI)</td><td>95.2 (70.7 to 99.3)</td></tr></table></td><td>Thank you for highlighting. Confidentiality marking removed.</td></tr>
<tr><td>Page 61, Section 3.7.1</td><td>Median OS from LIBRETTO-001 (in all analysis sets) is not published so should be</td><td>Please can the text and confidentiality highlighting be amended as follows:</td><td>Thank you for highlighting. Rather than amending the text, the EAG has applied confidentiality</td></tr>
</table>

<table>
<tr>
<td></td>
<td>marked as confidential.</td>
<td>Page 61, Section 3.7.4 of the EAG report states:

“median DoR and PFS were not reached; median OS was **********.”</td>
<td>marking to the whole phrase as follows:

EAR, Section 3.7.4:

**********</td>
</tr>
<tr>
<td>Table 21, Page 70, Section 3.10.5

Table 22, Page 71, Section 3.10.5</td>
<td>Results of the ITC of selpercatinib versus cabozantinib and BSC (based on EXAM) do not need to be marked as confidential, as these are published in Jen et al (2023)[7]</td>
<td>Please can all confidentiality highlighting on Table 21 and Table 22 of the EAG report be removed.

In addition, please can the confidentiality highlighting on the following sentences be removed:

“After weighting, the effective sample size for the LIBRETTO-001 trial any-line RET-mutant MTC population was 157.”

“Applying the MAIC methodology led to treatment effect estimates that favoured selpercatinib over cabozantinib and BSC even more strongly than those calculated using unadjusted indirect comparison methods.”</td>
<td>Thank you for highlighting. Additional text added.</td>
</tr>
<tr>
<td>Table 42, Page 103, Section 4.10</td>
<td>Values related to the QALY shortfall analysis do not need to be marked as confidential, in line with the highlighting adopted in the CS. In particular, the following values do not need to be marked as confidential:

• Expected remaining QALYs for the general population

• Total QALYs that people living with a condition would be</td>
<td>Please can the confidentiality highlighting be amended as follows:

<table>
<tr><th>Total QALYs for patients receiving current standard of care</th><th>Expected general population QALYs</th><th>Absolute QALY shortfall</th><th>Proportional QALY shortfall</th></tr>
<tr><td>Cabozantinib: 2.11</td><td rowspan="2">14.34</td><td>12.23</td><td>85.29%</td></tr>
<tr><td>BSC: 1.51</td><td>12.83</td><td>89.47%</td></tr>
<tr><td>Lenvatinib: 2.62</td><td rowspan="2">13.38</td><td>10.76</td><td>80.42%</td></tr>
<tr><td>BSC: 1.27</td><td>12.11</td><td>90.51%</td></tr>
</table>
</td>
<td>Thank you for highlighting. Confidentiality marking removed.</td>
</tr>
</table>

<table>
<tr><td></td><td>expected to have with current treatment
• Absolute QALY shortfall
• Proportional QALY shortfall</td><td></td><td></td></tr>
<tr><td>Table 54, Page 121, Section 6.2.1</td><td>The Company clarification questions base case ICER (x1.2 severity modifier applied) does not need to be marked as confidential, in line with the highlighting adopted in the CS.</td><td>Please can confidentiality highlighting in this table be amended as follows:
<table><tr><th>£/QALY (x1.2 modifier where relevant)</th><th>Change from base case</th></tr><tr><td>£29,713*</td><td>-</td></tr></table></td><td>This was not marked as confidential in the EAG report. No change required.</td></tr>
<tr><td>Page 134, Section 8.1.2</td><td>Details on the single patient with papillary thyroid cancer in LIBRETTO-321 do not need to be marked as confidential as these data are published in Zheng et al. (2022).</td><td>Please can the confidentiality highlighting be removed as follows:
“Furthermore, as shown in Table 66, there was only 1 patient with RET fusion-positive TC in the LIBRETTO-321 trial and evidence for patients with RET fusion-positive TC from this trial are therefore very limited. This patient had papillary thyroid cancer.”</td><td>Thank you for highlighing. Additional text added.</td></tr>
<tr><td>Table 69, Page 142, Section B.3.1</td><td>Values for ECT QT prolongation in the LIBRETTO-531 trial should be marked as confidential as these data are not published.</td><td>Please can the confidentiality highlighting be amended as follows:
<table><tr><td>ECG QT prolongation</td><td>**********</td><td>**********</td><td>**********</td><td>**********</td><td>**********</td></tr></table></td><td>Thank you for highlighting. Confidentiality marking added.</td></tr>
<tr><td>Page 142, Section 8.3.2</td><td>For consistency with the CS, when reporting data on discontinuation due to hypertension, the type of thyroid cancer that the patient</td><td>Please can the confidentiality highlighting be amended as follows:
“Only *** patient discontinued selpercatinib due to hypertension; this patient had RET-mutant MTC.”</td><td>Thank you for highlighting. Additional text added.</td></tr>
</table>

	had does not need to be marked as confidential.		

References

1. Hadoux J, Elisei R, Brose MS, et al. Phase 3 Trial of Selpercatinib in Advanced RET-Mutant Medullary Thyroid Cancer. New England Journal of Medicine 2023:Online ahead of print.
2. Young TA, Mukuria C, Rowen D, et al. Mapping Functions in Health-Related Quality of Life: Mapping from Two Cancer-Specific Health-Related Quality-of-Life Instruments to EQ-5D-3L. Med Decis Making 2015;35:912-26.
3. Fordham BA, Kerr C, de Freitas HM, et al. Health state utility valuation in radioactive iodine-refractory differentiated thyroid cancer. Patient preference and adherence 2015;9:1561.
4. Zheng X, Ji Q, Sun Y, et al. Efficacy and safety of selpercatinib in Chinese patients with advanced RET-altered thyroid cancers: results from the phase II LIBRETTO-321 study. Therapeutic Advances in Medical Oncology 2022;14:1-12.
5. Hadoux J, Elisei R, Brose MS, et al. Phase 3 trial of selpercatinib in advanced RET-mutant medullary thyroid cancer. NEJM. 2023;389:1851-1861.
6. Wirth LJ, Subbiah V, Worden F, et al. Updated safety and efficacy of selpercatinib in patients with RET activated thyroid cancer: Data from LIBRETTO-001. ESMO 2023:2229P.
7. Jen M-H, Kiiskinen U, Khanal M, et al. Matching Adjusted Indirect Comparison (MAIC) of Selpercatinib vs Cabozantinib in RET Mutation-positive Advanced Medullary Thyroid Cancer (MTC), In International Society for Pharmacoeconomics and Outcomes Research, Copenhagen, Denmark, 2023.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with advanced thyroid cancer or caring for a patient with advanced thyroid cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

NICE National Institute for Health and Care Excellence

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. Please type information directly into the form.

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. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 21 March.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with advanced thyroid cancer

Table 1 About you, advanced thyroid cancer, current treatments and equality

1. Your name	Kirstie Purnell
2. Are you (please tick all that apply)	☐ A patient with advanced thyroid cancer? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with advanced thyroid cancer? ☐ 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 and provide answers when 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 or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have not completed part 2 of the statement

6. What is your experience of living with advanced thyroid cancer? **If you are a carer (for someone with advanced thyroid cancer) please share your experience of caring for them**	Medullary thyroid cancer is a devastating disease. The problem with RET mutation-positive MTC is that it doesn't affect one person but numerous people in the same family. 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 is termed the 'index case' for our family. 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, and has never been the same since from an anxiety perspective. 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. My daughter has just completed her 4th year of treatment and my son approaches a similar milestone. They are currently living a relatively normal life and, most importantly, are in good health from a cancer point of view. They have regular monitoring and so far have not encountered any major side effects from the treatment. I asked each of my children for a statement about selpercatinib. My son says that he is glad that he has been able to have selpercatinib, it is easy to take and has not caused him any side effects. My daughter says
7a. What do you think of the current treatments and care available for advanced thyroid cancer 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 (for example, how they are given or taken, side effects of treatment, and any others) 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.
9a. If there are advantages of advanced thyroid cancer over current treatments on the NHS please describe these. For example, the effect 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 or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	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 <50 consistently. Her CEA has gone from 250 to around 8. My son's calcitonin came down from approximately 180 to around 3 i.e. 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). They have to attend hospital less than those having to have radiotherapy or even the more toxic chemotherapy agents. 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. Rather obviously and very importantly, they are alive and well – which highly likely would not have been the case if they had had to rely on the other treatment options.
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 effects you have heard about, please describe them and explain why	Genuinely, I am not aware of any disadvantages over current treatments.
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	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. Patients who may be deemed not fit for surgery, eg due to other health problems and anaesthetic risk, may still have a treatment option open to them. 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.
12. Are there any potential equality issues that should be taken into account when considering advanced thyroid cancer and selpercatinib? Please explain if you think any groups of people with this condition are particularly disadvantage 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 Find more general information about the Equality Act and equalities issues here.	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).
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: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Selpercatinib has completely the changed the prognosis for my two children (a 50% 5-year survival rate was quoted at diagnosis and that was for less advanced disease than my daughter has) and had a significant beneficial effect on our family as a whole.
- Selpercatinib is easy to take and requires minimal monitoring once stabilised.
- My children have had no side effects, to date, from taking selpercatinib.
- Other currently available treatment options for MTC have significant side effect profiles and are not very effective.
- Selpercatinib has allowed my children to attend school as a 'normal' child would, enabling them to access a good education, and take part in leisure activities without limitation.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 21 March.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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

NICE National Institute for Health and Care Excellence

Part 1: Treating advanced thyroid cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Jonathan Wadsley
2. Name of organisation	Sheffield Teaching Hospitals NHS Foundation Trust
3. Job title or position	Consultant Clinical Oncologist
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 advanced thyroid cancer? ☒ A specialist in the clinical evidence base for advanced thyroid cancer 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)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation 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)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links
8. What is the main aim of treatment for advanced thyroid cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aims of treatment in this situation are multiple- to control symptoms and improve quality of life, to stop progression of the disease, and to improve overall survival. The most important aim is to extend survival with good quality of life.

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)	In hierarchical order, clinically significant treatment responses would include- 1. An extension in overall survival of greater than 3 months 2. An extension in progression free survival of greater than 6 months 3. An improvement in symptom burden and quality of life- more difficult to quantify
10. In your view, is there an unmet need for patients and healthcare professionals in advanced thyroid cancer?	Yes, there is an unmet need. There is no curative treatment for this condition and prognosis is limited. Existing treatments, whilst they can delay progression of disease, are not proven to extend survival and are often associated with significant side effects which impair quality of life.
11. How is advanced thyroid cancer 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?	For advanced, progressive iodine refractory differentiated thyroid cancer, NICE currently recommends treatment with either sorafenib OR Lenvatinib (TA535). For advanced, progressive medullary thyroid cancer, NICE currently recommends treatment with cabozantinib (TA516) For patients with either of these conditions with identified RET alterations, Selpercatinib is currently available via the Cancer Drugs Fund as a second line treatment option (TA742)- ie after failure of treatment with the above drugs. The pathway of care is well defined. Molecular genetic testing for RET alterations in patients with advanced thyroid cancers is now well established in the UK, allowing suitable patients to be identified. The advantage of the proposal to bring Selpercatinib into the first line setting is that patients would then be treated with a drug associated with less toxicity and, at least in advanced medullary thyroid cancer, with evidence that first line treatment with this agent extends progression free survival (and probably overall survival) when compared with the current standard of care, cabozantinib (LIBRETTO-531 trial data).

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 clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The current proposal would mean that for patients with advanced thyroid cancers and evidence of RET alterations, Selpercatinib would be available as the first line treatment, rather than having to have previously had Sorafenib/Lenvatinib/Cabozantinib and progressed on prior treatment. The treatment will only be used in tertiary care, in specialist thyroid oncology clinics. No new facilities or equipment would be required since this is an oral drug treatment. Since the treatment is so much better tolerated than existing drug treatments, it is actually likely that supportive care requirements will be significantly less for patients on this drug.
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?	There is some evidence from the LIBRETTO-531 trial that treatment with Selpercatinib may extend length of life when compared with current standard of care for patients with advanced medullary thyroid cancer. The study was not powered to detect an overall survival benefit and this was not the primary endpoint, but the data do strongly suggest a trend in this direction. As yet unpublished data demonstrates that patients taking Selpercatinib spend significantly less time having bothersome side effects than patients on comparator treatments (Cabozanitinib or Vandetinib), and that HRQoL is significantly improved.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Selpercatinib is specifically indicated for patients with cancers that harbour RET alterations. There is no point in treating patients without these alterations.
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?	Since it is associated with significantly less toxicity, treatment with Selpercatinib is likely to be easier to use (and certainly no more difficult) than current standard of care treatments, which are associated with significant side effects which need

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	to be managed with supportive medications, and occasionally with hospital admission.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will need to be tested for presence of RET alterations (either fusions or mutations), but this testing is already readily available in England through the Genomic Laboratory Hubs, and the tests are listed in the Genomic Test Directory. Treatment with Selpercatinib will be continued whilst patients are deemed to be deriving clinical benefit, and not experiencing intolerable toxicity.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Beyond HRQoL measures, analyses have been undertaken to demonstrate that patients receiving Selpercatinib spend less time experiencing bothersome side effects, therefore likely requiring less supportive care.
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?	Having had some personal experience of using this drug, treating patients participating in the LIBRETTO-531 study, I would say that it does present a step change in the management of this patient group. Apart from the evidence demonstrating improved response rates, progression free survival and overall survival, the drug is so much better tolerated that patients are able to continue usual daily activities, often including continuing to work, where this was previously very unlikely to be possible due to the side effects associated with current standard of care treatments.

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?	As above, side effects are significantly less problematic than with current standard of care treatment and the LIBRETTO-531 trial has demonstrated an improvement in HRQoL with this treatment when compared with current standard of care.
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?	The LIBRETTO-531 trial does reflect the way that this drug would be used in UK clinical practice if approved under this proposal. The most important outcomes as described above are an improvement in overall survival, and improvement in progression free survival, and an improvement in HRQoL- all of these were measured in the LIBRETTO-531 trial. I am not aware of any adverse effects having been reported that were not uncovered in clinical trials, but experience with this drug outside of clinical trials is currently very limited.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Nothing beyond the LIBRETTO-001 and LIBRETTO-531 studies.
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance (cabozantinib, TA516; lenvatinib and sorafenib, TA535)?	No
23. How do data on real-world experience compare with the trial data?	I am not aware of any published real-world experience data.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	I am not aware of any equalities issues

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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is reliable evidence that Selpercatinib extends progression free survival when compared with current standard of care, at least for patients with RET mutant medullary thyroid cancer.
There is evidence suggesting a trend towards improved overall survival when compared with current standard of care for patients with RET mutant medullary thyroid cancer treated with Selpercatinib.
Treatment with Selpercatinib is associated with significantly less time spent with bothersome side effects than current standard of care treatment and is therefore associated with less need for supportive medications and with improved quality of life.
Click or tap here to enter text.
Click or tap here to enter text.

Thank you for your time.

Your privacy

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Single Technology Appraisal

Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132]

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send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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

Part 1: Treating advanced thyroid cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Kee Wong
2. Name of organisation	Eli Lilly
3. Job title or position	Consultant clinical oncologist
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 advanced thyroid cancer? ☒ A specialist in the clinical evidence base for advanced thyroid cancer 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)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation 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)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for advanced thyroid cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1) To improve or delay onset of symptoms related to disease progression whilst maintaining reasonable quality of life 2) To improve disease-specific survival

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)	1) Any reduction in disease burden leading to improvement in symptoms (even if it is below standard RECIST criteria of 30%). For example, reduction in biochemical markers such as Calcitonin in medullary thyroid cancer will lead to significant improvement in symptoms such as drug-resistant diarrhoea.
10. In your view, is there an unmet need for patients and healthcare professionals in advanced thyroid cancer?	Yes, there is an unmet need for advanced thyroid cancer. Current management for advanced or metastatic thyroid cancer are based on earlier clinical trials utilising multikinase inhibitors in all comers irrespective of mutational landscapes. Whilst these treatments have been shown to have some efficacy, patients experience significant side effects which invariably lead to frequent treatment interruption and dose reduction. With the advent of molecular profiling, there needs to be a shift towards targeted therapy which there are good data now to demonstrate much high efficacy and more durable response with better tolerability. Moreover, whilst rare in numbers, patients who harbour germline RET alteration and present with advanced/metastatic thyroid cancer are paediatric patients (<18 year old) where there are no standard current care. These patients are currently managed using drug obtained via compassionate use programme from drug company.
11. How is advanced thyroid cancer 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?	Advanced thyroid cancer is currently treated mainly with surgery followed by either radioiodine treatment for differentiated thyroid cancer (DTC) or surveillance for medullary thyroid cancer (MTC). External beam radiotherapy is only used in selective case where the disease is iodine refractory and there is anticipated threat to surrounding critical structures. In the event of distant metastasis, patients are kept under close surveillance until the disease starts to progress more rapidly/patient becomes more symptomatic. These would then be indications to initiate multikinase inhibitors (current first line treatment for DTC is Lenvatinib and Cabozantinib for MTC). These practices are standard across NHS and ESMO thyroid cancer guidelines are being used whilst UK based guidelines e.g. BTA are being updated. The impact of this technology appraisal would only impact those who harbours RET alterations and not the whole population.

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 clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes, will be used in the same way as current care in NHS except being used as 1st line rather than 2nd line treatment for those patients with RET alteration.
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?	Yes. Patients are anticipated to do better in term of treatment efficacy, durability, tolerability and quality of life with this targeted therapy compared to current care (evidenced by the randomised controlled trial and clinician's 'real-world' experience)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is only for patients with advanced thyroid cancers who harbours RET alteration (either germline or somatic) where the technology will be more effective.
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)	This treatment has no additional practical implication for either patient or healthcare professionals. The clinic visits/tests required are similar to current care initially and in fact, may lessen in frequency once patients are established on treatment given better tolerability.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients need to have RET alterations to quality for this treatment. Molecular testing is now considered standard-of-care for these advanced thyroid cancers and available through regional genomic laboratory hubs (GLHs).
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The method of administration with this technology is oral which is the same with current care, but it is anticipated that patients require less frequent hospital visits for monitoring once they are established on the treatment compared to current care. In addition, patients are less likely to require supportive medications to manage treatment associated side effects i.e. more cost saving. Otherwise, the health-related benefits in term of quality of life should be captured with QALY.
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?	Yes, this treatment is a 'game-changer' in the era of personalised medicine/targeted therapy. Current care is less effective and more importantly, less well tolerated than the technology with more frequent dose reduction and treatment discontinuation. Patients often put up with side effects that come with current care and these have significant negative impact on both their physical and emotional functionality. Also, as stated above, there needs to be treatment option available for paediatric patients with RET alterations who present with advanced/metastatic thyroid cancer.
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?	As above. This technology still has side effect profiles expected of drug of its kind but much better tolerated with less negative impact on patient's quality of life.
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?	Yes, the randomised controlled trials conducted reflect current UK clinical practice. The most important outcomes were disease progression free survival as well as tolerability of the treatment. These were measured in the trials. The surrogate outcome reported also adequately predict long-term clinical outcomes e.g. overall survival. This technology has already been in clinical use in the second

• 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?	line setting based on prior registrational studies and the adverse effects profile seen are in line with what was reported in the trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance (cabozantinib, TA516; lenvatinib and sorafenib, TA535)?	No.
23. How do data on real-world experience compare with the trial data?	With regards to real world experience for current standard care, there are publications outlining substantial disease and treatment burden in term of patient reported outcomes, highlighting the need for targeted therapy. Regarding real world experience of the technology, there are several case series in the literature reporting similar observation with the trial data.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this 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. Please state if you think this evaluation could	There is no equality issues here as this is a self-selected group based on presence of either germline or somatic mutation.

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The technology is more effective and durable than current standard care in reducing both tumour and symptom burden in patients with advanced thyroid cancer.

The technology is better tolerated than current standard care and may lead to less need for supportive medication to manage side effects

The technology is likely to lead to reduced frequency of clinic visits and tests for long-term monitoring

The technology meets the unmet need for paediatric patients with RET alteration

The technology is anticipated to prolong life expectancy for certain patients.

Thank you for your time.

Your privacy

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APPENDIX (9 APRIL 2024)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Selpercatinib for untreated advanced thyroid cancer with *RET* alterations [ID6132]

Appendix: scenario analyses removing selpercatinib, cabozantinib and lenvatinib relative dose intensity multipliers

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136152

Completed 09 April 2024

CONTAINS CON DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ALL TABLES IN THIS APPENDIX ARE CONFIDENTIAL

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of selpercatinib for untreated advanced *RET*-mutant MTC and untreated advanced *RET* fusion-positive TC, the company (Eli Lilly) developed an economic model using Microsoft Excel.

In the company submission (CS), base case cost effectiveness results were presented for the comparison of selpercatinib versus cabozantinb or versus best supportive care (BSC) for the *RET*-mutant MTC population and selpercatinib versus lenvatinib or versus BSC for the *RET* fusion-positive TC population. Results were generated using the proposed Patient Access Scheme (PAS) price for selpercatinib and list prices from the British National Formulary (BNF) were used for cabozantinib and lenvatinib. As BSC was assumed to consist of routine care and monitoring for both the *RET*-mutant MTC and *RET* fusion-positive TC populations, no drug prices were used.

This appendix includes deterministic results for scenario analyses that remove treatment relative dose intensity (RDI) multipliers.

Removal of RDI multipliers

During the PMB, additional scenarios that assumed there would no treatment cost savings from missed/interrupted doses were requested. Therefore, the EAG has presented scenario results that were generated by removing selpercatinib, cabozantinib and lenvatinib RDI multipliers.

As cabozantib and lenvatinib have the same price for all doses, dose reductions do not result in treatment cost reductions. However, selpercatinib has different prices for different doses; this means that dose reductions result in treatment cost reductions. The EAG has therefore presented additional scenario results that were generated by only removing cabozantinib and lenvatinib RDI multipliers. The selpercatinib RDI multiplier has not been removed as there may be treatment cost savings from dose reductions.

The company base case deterministic cost effectiveness results for the comparisons of selpercatinib versus cabozantinib and lenvatinib are presented in Table 1 and Table 2, respectively, alongside the results of each EAG revision and the EAG exploratory scenarios.

Table 1 Deterministic results for the *RET*-mutant MTC population (selpercatinib versus cabozantinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier where relevant)	£/QALY (x1.2 modifier where relevant)	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£89,900**	**2.080**	[redacted]	[redacted]	**£29,713***	**-**
R1) Stratified spline 1 knot distribution to extrapolate cabozantinib OS	[redacted]	[redacted]	£90,573	2.206	[redacted]	[redacted]	£36,666	£6,953
R2) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£89,900	2.417	[redacted]	[redacted]	£35,306	£5,593
R3) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£89,900	2.080	[redacted]	[redacted]	£36,554*	£6,841
R4) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£89,900	2.080	[redacted]	[redacted]	£27,047*	-£2,666
R5) Selpercatinib and cabozantinib RDI removed	[redacted]	[redacted]	£116,815	2.080	[redacted]	[redacted]	£36,646*	£6,933
R6) Cabozantinib RDI only removed	[redacted]	[redacted]	£116,815	2.080	[redacted]	[redacted]	£23,963*	-£5,750
B. EAG alternative scenario (R1-R2)	[redacted]	[redacted]	**£90,573**	**2.594**	[redacted]	[redacted]	**£36,791**	**£7,078**
C. EAG exploratory scenarios								
C1. R1-R3	[redacted]	[redacted]	**£90,573**	**2.594**	[redacted]	[redacted]	**£49,853**	**£20,140**
C2. R1-R2, R4	[redacted]	[redacted]	**£90,573**	**2.594**	[redacted]	[redacted]	**£31,997**	**£2,284**
C3. R1-R2, R5	[redacted]	[redacted]	**£117,572**	**2.594**	[redacted]	[redacted]	**£45,394**	**£15,681**
C4. R1-R2, R6	[redacted]	[redacted]	**£117,572**	**2.594**	[redacted]	[redacted]	**£29,615**	**-£98**

*1.2x severity modifier applied

EAG=External Assessment Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 2 Deterministic results for *RET* fusion-positive TC population (selpercatinib versus lenvatinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification revised base case	[redacted]	[redacted]	**£96,507**	**2.622**	[redacted]	[redacted]	**£36,329**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£96,507	2.988	[redacted]	[redacted]	£35,130	-£1,199
R2) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£96,507	2.622	[redacted]	[redacted]	£46,063	£9,734
R3) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£96,507	2.622	[redacted]	[redacted]	£32,221	-£4,108
R4) Selpercatinib and lenvatinib RDI removed	[redacted]	[redacted]	£131,345	2.622	[redacted]	[redacted]	£42,828	£6,499
R5) Lenvatinib RDI only removed	[redacted]	[redacted]	£131,345	2.622	[redacted]	[redacted]	£22,472	-£13,857
B. EAG alternative scenario (R1)	[redacted]	[redacted]	**£96,507**	**2.988**	[redacted]	[redacted]	**£35,130**	**-£1,199**
C. EAG exploratory scenarios								
C1. R1, R2	[redacted]	[redacted]	**£96,507**	**2.988**	[redacted]	[redacted]	**£50,131**	**£13,802**
C2. R1, R3	[redacted]	[redacted]	**£96,507**	**2.988**	[redacted]	[redacted]	**£29,756**	**-£6,573**
C3. R1, R4	[redacted]	[redacted]	**£131,345**	**2.988**	[redacted]	[redacted]	**£41,414**	**£5,085**
C4. R1, R5	[redacted]	[redacted]	**£131,345**	**2.988**	[redacted]	[redacted]	**£21,730**	**-£14,599**

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; OS=overall survival; QALYs=quality adjusted life year; RDI=relative dose intensity; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

NON-CONFIDENTIAL APPENDIX 3

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Selpercatinib for untreated advanced thyroid cancer with *RET* alterations [ID6132]

Non-confidential Appendix 3: NICE ACM1 preferred assumptions

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136152

Completed 23 April 2024

CONTAINS CON DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of selpercatinib for untreated advanced *RET*-mutant MTC and untreated advanced *RET* fusion-positive TC, the company (Eli Lilly) developed an economic model using Microsoft Excel.

In the company submission (CS), base case cost effectiveness results were presented for the comparison of selpercatinib versus cabozantinb or versus best supportive care (BSC) for the *RET*-mutant MTC population and selpercatinib versus lenvatinib or versus BSC for the *RET* fusion-positive TC population. Results were generated using the proposed Patient Access Scheme (PAS) price for selpercatinib and list prices from the British National Formulary (BNF) were used for cabozantinib and lenvatinib. As BSC was assumed to consist of routine care and monitoring for both the *RET*-mutant MTC and *RET* fusion-positive TC populations, no drug prices were used.

This appendix includes base case pairwise cost effectiveness results generated by the company clarification model and External Assessment Group (EAG) revisions, for the comparison of selpercatinib versus cabozantinib (*RET*-mutant MTC) and selpercatinib versus lenvatinib (*RET* fusion-positive TC). Pairwise cost effectiveness results for the comparison of selpercatinib versus BSC are presented in Table 56 and Table 57 of the EAR (*RET*-mutant MTC population) and in Table 62 and Table 63 (*RET* fusion-positive TC population).

RET-mutant MTC population

This appendix includes results for the NICE Appraisal Committee Meeting 1 (ACM1) preferred scenario, which includes the following revisions:

- stratified spline 1 knot distribution used to extrapolate cabozantinib OS (R1)
- mapped health state utility values (LIBRETTO-001 trial EORTC-QLQ-C30 data, any-line RET fusion-positive TC population) (R2)
- cabozantinib RDI removed (R3).

Exploratory scenarios relating to selpercatinib OS extrapolations, evaluated through the following revisions:

- pessimistic selpercatinib OS extrapolation using an adjustment factor of 3.5 applied at 5 years (R4)
- optimistic selpercatinib OS extrapolation using an adjustment factor of 1.5 applied at 5 years (R5).

RET fusion-positive TC population

The revisions included in the NICE ACM1 preferred scenario for the *RET* fusion-positive TC population are:

- mapped health state utility values (LIBRETTO-001 trial EORTC-QLQ-C30 data, any-line RET fusion-positive TC population) (R1)
- lenvatinib RDI removed (R2).

Exploratory scenarios relating to selpercatinib OS extrapolations, evaluated through the following revisions:

- pessimistic selpercatinib OS extrapolation using an adjustment factor of 1.5 applied at 18 months (R3)
- optimistic selpercatinib OS extrapolation using an adjustment factor of 0.9 applied at 5 years (R4).

The company base case deterministic cost effectiveness results for the comparisons of selpercatinib versus cabozantinib and versus lenvatinib are presented in **Error! Not a valid bookmark self-reference.** and Table 3, respectively, alongside the results of each EAG revision, the ACM1 Committee preferred scenario and exploratory scenarios. Probabilistic pairwise cost effectiveness results are presented in Table 3 and Table 4. Fully incremental analyses for the ACM1 Committee preferred assumptions are presented in Table 5 and Table 6.

Table 1 Deterministic results for the *RET*-mutant MTC population (selpercatinib versus cabozantinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£89,900**	**2.080**	[redacted]	[redacted]*	**£29,713***	**-**
R1) Stratified spline 1 knot distribution to extrapolate cabozantinib OS	[redacted]	[redacted]	£90,573	2.206	[redacted]	[redacted]	£36,666	£6,953
R2) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£89,900	2.417	[redacted]	[redacted]	£35,306	£5,593
R3) Cabozantinib RDI removed	[redacted]	[redacted]	£116,815	2.080	[redacted]	[redacted]*	£23,963*	-£5,750
R4) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£89,900	2.080	[redacted]	[redacted]*	£36,554*	£6,841
R5) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£89,900	2.080	[redacted]	[redacted]*	£27,047*	-£2,666
B. Committee preferred scenario (R1-R3)	[redacted]	[redacted]	**£117,572**	**2.594**	[redacted]	[redacted]	**£29,615**	**-£98**
C. EAG exploratory scenarios								
C1. R1-R4	[redacted]	[redacted]	**£117,572**	**2.594**	[redacted]	[redacted]	**£39,918**	**£10,205**
C2. R1-R3, R5	[redacted]	[redacted]	**£117,572**	**2.594**	[redacted]	[redacted]	**£25,829**	**-£3,884**

*1.2x severity modifier applied
EAG=External Assessment Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; OS=overall survival; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 2 Probabilistic results for the RET-mutant MTC population (selpercatinib versus cabozantinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Cabozantinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£89,785**	**2.107**	[redacted]	[redacted]*	**£29,877***	**-**
B. Committee preferred scenario (R1-R3)	[redacted]	[redacted]	**£117,653**	**2.602**	[redacted]	[redacted]	**£30,782**	**£905**

*1.2x severity modifier applied
EAG=External Assessment Group; =incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection

Table 3 Deterministic results for *RET* fusion-positive TC population (selpercatinib versus lenvatinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£96,507**	**2.622**	[redacted]	[redacted]	**£36,329**	
R1) Mapped health state utility values from LIBRETTO-001 trial EORTC-QLQ-C30 data (any-line *RET* fusion-positive TC population)	[redacted]	[redacted]	£96,507	2.988	[redacted]	[redacted]	£35,130	-£1,199
R2) Lenvatinib RDI removed	[redacted]	[redacted]	£131,345	2.622	[redacted]	[redacted]	£22,472	-£13,857
R3) Pessimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£96,507	2.622	[redacted]	[redacted]	£46,063	£9,734
R4) Optimistic selpercatinib OS extrapolation	[redacted]	[redacted]	£96,507	2.622	[redacted]	[redacted]	£32,221	-£4,108
B. Committee preferred scenario (R1-R2)	[redacted]	[redacted]	**£131,345**	**2.988**	[redacted]	[redacted]	**£21,730**	**-£14,599**
C. EAG exploratory scenarios								
C1. R1-R3	[redacted]	[redacted]	**£131,345**	**2.988**	[redacted]	[redacted]	**£30,544**	**-£5,785**
C2. R1-R2, R4	[redacted]	[redacted]	**£131,345**	**2.988**	[redacted]	[redacted]	**£18,574**	**-£17,755**

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; OS=overall survival; QALYs=quality adjusted life year; RDI=relative dose intensity; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells

Table 4 Probabilistic results for RET fusion-positive TC population (selpercatinib versus lenvatinib), PAS price for selpercatinib

Scenario/EAG revisions	Selpercatinib		Lenvatinib		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	Change from base case
A. Company clarification base case	[redacted]	[redacted]	**£96,510**	**2.631**	[redacted]	[redacted]	**£36,347**	**-**
B. Committee preferred scenario (R1-R2)	[redacted]	[redacted]	**£131,415**	**2.957**	[redacted]	[redacted]	**£21,868**	**-£14,479**

EAG=External Assessment Group; =incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life year; *RET*=rearranged during transfection

Table 5 ACM1 Committee preferred scenario probabilistic results (fully incremental analysis) for *RET*-mutant MTC population, no severity modifiers applied, PAS price for selpercatinib and cabozantinib*

Treatment	Total costs	Total QALYs	ICER per QALY gained
BSC	£17,111	1.868	-
Cabozantinib	£117,653	2.602	Extendendly dominated
Selpercatinib	[redacted]	[redacted]	£48,682

* No modifiers applied when calculating ICERs per QALY gained; however, the comparison of selpercatinib versus BSC is eligible for a 1.2x modifier
BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MTC=medullary thyroid cancer; PAS=Patient Access Scheme; QALYs=quality adjusted life years; *RET*=rearranged during transfection
Source: Company clarification model with EAG revisions

Table 6 ACM1 Committee preferred scenario probabilistic results (fully incremental analysis) for *RET* fusion-positive TC population, no severity modifiers applied, PAS prices for selpercatinib and lenvatinib*

Treatment	Total costs	Total QALYs	ICER per QALY gained
BSC	£16,053	1.623	-
Lenvatinib	£131,415	2.957	Extendendly dominated
Selpercatinib	[redacted]	[redacted]	£43,896

* No modifiers applied when calculating ICERs per QALY gained; however, the comparison of selpercatinib versus BSC is eligible for a 1.2x modifier
BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years; *RET*=rearranged during transfection; TC=thyroid cancer originating in the follicular cells
Source: Company clarification model with EAG revisions

Table 7 Results from the QALY shortfall analyses, ACM1 committee preferred scenario

Population	Total QALYs for patients receiving current standard of care in Committee preferred scenario (deterministic value)	Expected general population QALYs	Absolute QALY shortfall	Proportional QALY shortfall	Severity modifier
RET-mutant MTC	Cabozantinib: 2.59	14.33*	11.74	81.92%	1
	BSC: 1.91		12.42	86.67%	1.2
RET fusion-positive TC	Lenvatinib: 2.99	13.38	10.39	77.65%	1
	BSC: 1.65		11.73	87.67%	1.2

*Calculated using MAIC-adjusted sex and age values as confirmed by the company in Issue 1 of the FAC