NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for advanced thyroid cancer with RET alterations after treatment with a cancer drug in people 12 years and over (managed access review of TA742) [ID6288]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Eli Lilly:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Thyroid Foundation and Butterfly Thyroid Cancer Trust

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews (KSR)

5. **External Assessment Group response to factual accuracy check of EAR**

6. **NHS England Systemic Anti-Cancer Therapy (SACT) dataset report**

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 treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]

Document B

Company evidence submission

April 2024

File name	Version	Contains confidential information	Date
ID6288_Selpercatinib in TC _Document B_Final_12Apr24 [CON]	Final	Yes	12th April 2024

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Tables and figures

Tables

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Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine transaminase
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 criterion
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
CAP	College of American Pathologists
CBR	Clinical benefit rate
CDF	Cancer Drug's Fund
CEA	Carcinoembryonic antigen
CHMP	Committee for Medicinal Products for Human Use
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost utility analysis
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
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European public assessment report

Abbreviation	Definition
FISH	Fluorescence in situ hybridization
FTC	Follicular thyroid cancer
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IEC/ISO	International Organization for Standardisation/Independent Ethics Committee
IPD	Individual patient-level data
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LPS	Lansky performance score
LTFU	Long term follow-up
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare Regulatory Agency
MKI	Multi-kinase inhibitor
MRI	Magnetic resonance scan
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NA	Not applicable
NCI	National Cancer Institute
NE	Not estimable
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
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
PDTC	Poorly differentiated thyroid cancer
PD	Progressed disease
PF	Progression free
PFS	Progression free survival
PPI	Proton pump inhibitors
PPPY	Per-patient per-year
PR	Partial response

Abbreviation	Definition
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Papillary thyroid cancer
QALY	Quality-adjusted life year
RAI	Radioactive iodine therapy
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
RPSFT	Rank Preserving Structural Failure Time
RP2D	Recommended Phase II dose
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCHARR	Sheffield Centre for Health and Related Research
SFU	Safety follow-up
SLR	Systematic literature review
SRC	Safety review committee
TA	Technology appraisal
TC	Thyroid cancer
TEAE	Treatment-emergent adverse events
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
TTD	Time to treatment discontinuation
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*

Following the recommendation of selpercatinib for use within the Cancer Drug's Fund (CDF) (TA742), the objective of this appraisal is to determine the clinical and cost-effectiveness of selpercatinib, in order to transition from reimbursement via the CDF to routine commissioning in UK clinical practice, 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 after cabozantinib or vandetanib
- For advanced *RET* fusion-positive thyroid cancer (TC) in people aged 12 years and older who require systemic therapy after sorafenib or lenvatinib

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 advanced *RET*-mutant MTC who require systemic therapy who have 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 "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET* fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate)", as this submission covers only those patients with advanced *RET* fusion-positive TC who require systemic therapy who have previously received lenvatinib or sorafenib.

It should also be noted that TA742 only covered adults with *RET*-fusion positive TC who were previously treated with lenvatinib or sorafenib; the licence for selpercatinib in this indication is currently being expanded to adults and adolescents aged 12 years and over. Marketing authorisation for this licence expansion has been received from the European Medicines Agency (EMA), and marketing authorisation for the Medicines and Healthcare Regulatory Agency (MHRA) is expected in [redacted].[2] The MHRA licensed indication for selpercatinib is anticipated to reflect the EMA licensed indication.[2]

This submission only considers patients with *RET*-altered TC and MTC who require systemic therapy after cabozantinib or vandetanib (MTC), or after sorafenib or lenvatinib (TC).[3] The remaining populations within the licensed indications (i.e., patients who have not previously received systemic therapy) are currently undergoing appraisal as part of the ongoing submission for selpercatinib in untreated *RET*-altered TC and MTC (ID6132).

The decision problem addressed within this submission, which is aligned 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	• People with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib • People with advanced *RET* mutation-positive MTC who require systemic therapy after cabozantinib or vandetanib	***RET*-fusion positive TC:** Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib and/or sorafenib ***RET*-mutant MTC:** Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib	***RET*-fusion positive TC:** Not applicable (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
Subgroups	If the evidence allows, subgroups based on the following will be considered: • Type of thyroid cancer within advanced *RET* fusion-positive TC (such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma) • Specific type of *RET* alteration (within *RET* fusion-positive TC or *RET*-mutation positive MTC) may need to be considered, as some types of *RET* genetic alteration may be more or less sensitive to selpercatinib	The following clinical efficacy subgroup analyses have been presented in the submission: ***RET* fusion-positive TC** • *RET* fusion type (objective response rate [ORR] and duration of response [DOR]) • Type of follicular TC (ORR only) ***RET*-mutant MTC** • *RET* mutation type (ORR and DOR) No subgroup analyses were considered in the cost-effectiveness evaluation.	It should be noted that although subgroup analyses are presented for these subgroups, results are limited by small patient numbers, particularly for the *RET* fusion-positive TC population (Section B.2.7) Due to particularly small patient numbers by type of follicular TC and type of *RET*-mutation, no subgroup analyses were considered in the cost-effectiveness evaluation
Comparator(s)	***RET*-fusion positive TC:** • Best supportive care (BSC) or palliative care	***RET*-fusion positive TC:** • BSC	NA – in line with the NICE final scope

	***RET*-mutant MTC:** • BSC or palliative care	***RET*-mutant MTC:** • BSC	
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 ORR **Key secondary endpoints** • DOR • Time to response and time to best response • Clinical benefit rate (CBR) • OS • PFS • AEs of treatment • HRQoL	NA – in line with the NICE final scope
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 (QALY) 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	The economic analysis has been provided in line with the NICE reference case **Outcomes:** The incremental cost-effectiveness ratio (ICER) of selpercatinib versus each comparator was evaluated in terms of an incremental cost per QALY gained **Model time horizon:** 35 years in base case **Model perspective:** The analysis was conducted from the perspective of the NHS and Personal Social Services **Commercial arrangements:** A confidential Patient Access Scheme (PAS) of [redacted]% has been provided alongside this submission. The commercial arrangements for	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 the cost-effectiveness results

	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/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	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.[4]	
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; MTC: medullary thyroid cancer; NA: not applicable; 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.

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 *RET*-fusion positive TC and *RET*-mutant MTC previously treated with systemic therapy 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 the treatment of patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib was granted by the MHRA in March 2021.[1] The marketing authorisation was then expanded to cover both the prior systemic therapy and systemic therapy naïve MTC populations in February 2023.[5] ***RET* fusion-positive TC** A conditional marketing authorisation application for the treatment of adults with *RET*-fusion positive TC who had been previously treated with lenvatinib or sorafenib was granted by the MHRA in March 2021. Marketing authorisation for the licence expansion of selpercatinib for the treatment of patients aged 12 years and older with *RET*-fusion positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate) is expected from the MHRA 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.[3, 6]
Indications and any restriction(s) as described in the SmPC	Marketing authorisations for selpercatinib relevant to the populations of interest in this submission are as follows: • "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC" • (anticipated MHRA marketing authorisation wording) "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET* fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate)" **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.[7] 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.[8, 9]
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 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: EMA: European Medicines Agency; EU: European Union; FISH: fluorescent in situ hybridisation; MHRA: Medicines and Healthcare products Regulatory Agency; 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)[10], Mulligan *et al.* (2018)[11]; 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.[12]
- 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%.[13]
    - 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.[14]
    - 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. In a study including 496 patients with PTC, *RET* fusions were identified in 6.8% of the patient population.[15] However, *RET* fusions are uncommon in other types of follicular TCs.[11, 16] 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.[17]
- While TC is associated with a generally good prognosis, metastatic TC demonstrates a poor one-year survival rate of 77%.[18] Survival is partly dependent on subtype of TC; five-year survival for distant stage TC ranges from 74% for PTC to just 4% for distant stage ATC.[19]
- In addition to facing a poor prognosis, patients with TC have poorer HRQoL than the general population due to a substantial symptom and disease burden.[20, 21] Key concerns include fatigue, pain, fear of recurrence, physical and mental exhaustion, employment, and lumps in the neck.[22] MTC is associated with additional debilitating symptoms, including severe diarrhoea, Cushing syndrome, bone pain, lethargy and weight loss, as well as distant metastases.[23, 24] These symptoms may lead to workplace absence and lost productivity.[25]

Summary of the diagnostic and treatment pathway

- Confirmation of *RET*-testing is 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.[7, 9]
- For patients with MTC, following surgery, cabozantinib is recommended for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC (TA516).[26]
- For patients with DTC, 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).[27]
    - As patients with ATC are ineligible to receive treatment with lenvatinib or sorafenib, selpercatinib is currently available for patients with *RET* fusion-positive ATC who have not received prior MKI therapy via the CDF.[28]
- For patients with advanced *RET*-altered MTC and TC whose disease has progressed following prior systemic therapy, BSC represents the only routinely available treatment option. Selpercatinib is currently available via the CDF for these patients, but should selpercatinib not become available via routine commissioning, BSC represents the only alternative option.[28]

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 whose disease has progressed after cabozantinib and/or vandetanib" and "people aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy and whose disease has progressed after sorafenib and/or lenvatinib".
- The relevant comparator for selpercatinib in both the advanced *RET*-mutant MTC population and advanced *RET*-fusion positive TC population is BSC.
- Should selpercatinib not become available via routine commissioning as an option following prior systemic therapy, BSC represents the only alternative treatment option; patients with advanced thyroid cancer whose disease has progressed following treatment with multi-kinase inhibitors (MKIs) who are receiving BSC face a poor prognosis. As such, there is a high unmet need for selpercatinib to remain an option via routine commissioning in UK. With highly specific and potent targeting of *RET* alterations, selpercatinib offers an effective treatment alternative to BSC, with a tolerable safety profile.

B.1.3.1 Disease overview

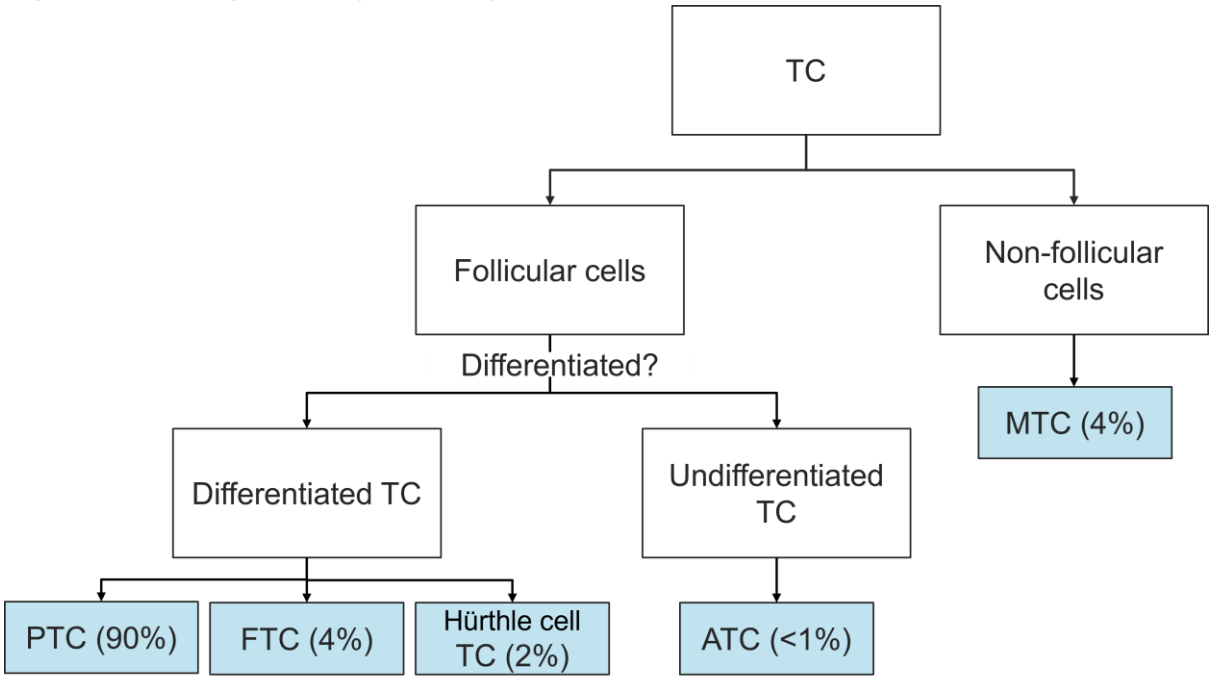
This submission focuses on the following indications:

- People aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy after cabozantinib and/or vandetanib
- People aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib and/or lenvatinib

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: PTC, FTC, Hürthle cell, ATC and MTC, 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,[13]; Roy et al. 2013.[14]

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.[13] Hürthle cell cancers are a rare type of DTC accounting for approximately 2% of TC cases.[13] 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.[14]

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] The two subtypes of MEN2, MEN2A and MEN2B, differ by disease severity and associated phenotypes, with the generally less severe MEN2A subtype representing >95% of cases.[11]

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.[11] 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.[11, 16] In a large study including 496 patients with PTC, *RET* fusions were identified in 6.8% of the patient population.[15] *RET* alterations in *RET* fusion-positive PTC, termed *RET*/PTC, are most typically acquired during a person's lifetime.[17] 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.[34]

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.[35] 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.[36] 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.[37] Other oncogenic mutations have been implicated in papillary, follicular and anaplastic TCs, such as *TRK*, *RAS*, *BRAF*, *PPARG* and *p53*.[38] There is currently no consensus regarding the impact of *RET*-fusions on prognosis for patients with TC.[39-42]

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.[17] 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.[11, 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.[11] 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.[11, 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.[12]

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.[12] 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).[12, 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 in patients who have received prior systemic therapy. 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%.[12, 18, 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.[19]

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.[11] Sporadic *RET* mutations correlate with a more aggressive disease phenotype,[17] while hereditary MTC severity ranges depending on the specific mutation.[17]

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.[41, 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.[11] 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.[39, 40] *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.[41, 42]

In contrast, somatic mutations of *RET* correlate with a poor prognosis versus *RET* wild-type tumours.[11, 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 routinely available treatment options

Survival of patients with advanced stage TC is known to be poor.[18, 19] However, the available literature investigating the survival of patients with *RET*-altered, advanced thyroid cancer in patients that have received prior systemic therapy is sparse. Some evidence is available from the EXAM trial, a Phase III trial investigating cabozantinib versus placebo in progressive MTC. However, OS data are not reported for *RET*-mutant patients specifically, and reported data include both patients who are systemic therapy-naïve and those who have received prior systemic therapy. Taking the placebo arm of this trial as a suitable proxy for patients receiving BSC, median OS in all patients (N=111) or those with *RET* M918T-positive disease (N=45) was 21.1 months and 18.9 months, respectively.[54] Considering that the EXAM trial enrolled a combination of patients who had either been previously treated (N=44 [20.1%]) with TKI inhibitors, or who were treatment naïve to TKI inhibitors (N=171 [78.1%]), and that *RET* mutations are known to correlate with a worse prognosis when compared to *RET* wild-type MTC, the survival of patients with previously treated advanced, *RET*-mutant MTC may be worse than indicated by data from EXAM.[11, 32, 54]

The Phase III SELECT trial provides survival data for patients with progressive TC who had received up to one prior treatment with a TKI. Crossover from the placebo to the lenvatinib trial arm was permitted at disease progression, however, rank-preserving structural failure time (RPSFT) adjusted OS data are available for the placebo arm (N=131). Median OS for patients receiving placebo (considered a proxy for BSC) was 34.5 months (95% CI: 21.7, not estimable [NE]).[27] However, these data are not in a *RET* fusion-positive subgroup and include some patients who are systemic therapy naïve; just n=27/131 [20.6%] patients had previously received a TKI in the placebo arm.[55] As such, survival for patients with previously treated, advanced *RET* fusion-positive TC may be worse than these data indicate.

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.[23] 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.[24] Debilitating symptoms associated with MTC (for example, severe diarrhoea) may lead to workplace absence and lost productivity.[25]

The humanistic burden of *RET*-altered thyroid cancer in patients previously treated with MKIs 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 or treatment line. 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.[20] 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.[22] 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.[21]

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.[27] 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.[3]

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 particularly 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 are often accompanied by post-surgical complications. This may have a substantial effect on patients' HRQoL and mental health, thus highlighting the importance of maintaining access to selpercatinib for these patients.[3] 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. Furthermore, the disease burden for patients with *RET*-altered thyroid cancer who have experienced disease progression following prior systemic therapy is likely to be even greater than systemic therapy naïve patients.

Economic burden

There are a lack of published data on the economic burden of *RET*-altered thyroid cancer following prior systemic therapy. 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.[22] 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 and available through the CDF for:

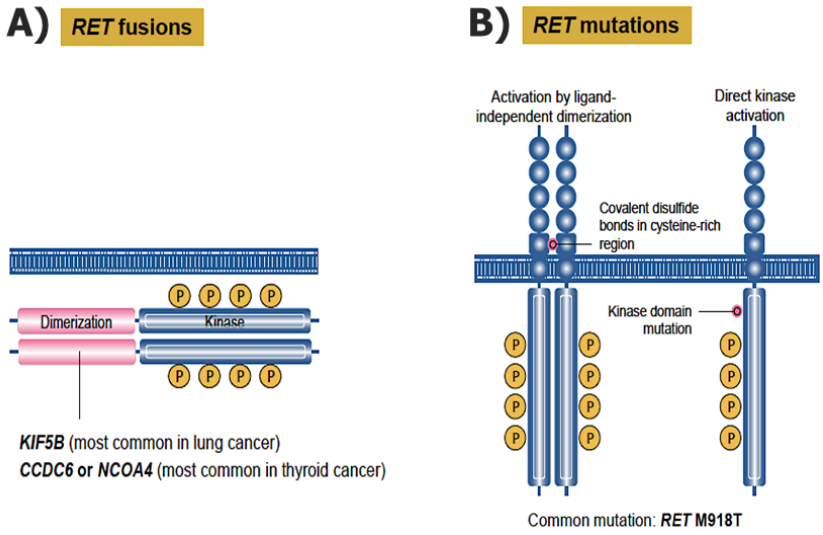
- Adults with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with sorafenib and/or lenvatinib (TA742)[3]
- People 12 years and older with advanced *RET*-mutant MTC who require systemic therapy after cabozantinib and/or vandetanib (TA742)[3]

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”.[1] The anticipated MHRA licensed indication for the TC population covered by this submission is “as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate)”; EMA marketing authorisation in this population has already been received.[2]

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.[11] 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]

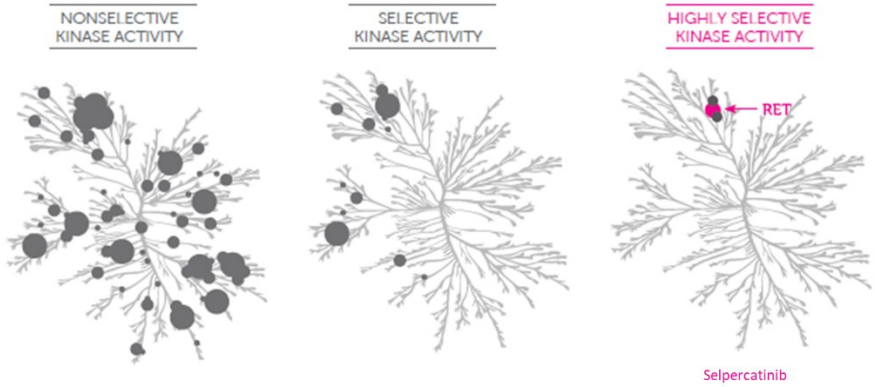
Selpercatinib targeting within the kinome (the complete set of protein kinases encoded within the genome) is displayed in Figure 3. In contrast to MKIs, which are non-selective and thus can be associated with off-target effects, selpercatinib is highly selective for *RET*, *RET*-fusion and *RET*-mutant 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)[10]

Figure 3: Kinome selectivity of selpercatinib



Abbreviations: RET; rearranged during transfection
Source: Drilon et al. (2018)[10]

B.1.3.3 Clinical pathway of care

Treatment guidelines for the management of thyroid cancer in the UK include those published by NICE (NG230), the UK National Multidisciplinary Guidelines and the British Thyroid Association.[28, 38, 64] 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) and cabozantinib for treating MTC (TA516).[26, 27] NICE also evaluated vandetanib for the first-line treatment of MTC (TA550), and cabozantinib for second-line treatment of DTC following lenvatinib and sorafenib (TA928).[65, 66] However, negative recommendations were issued for both appraisals.

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).[3] Selpercatinib is currently undergoing evaluation as a treatment for systemic therapy naïve patients with advanced *RET* fusion-positive TC and advanced *RET*-mutant MTC (ID6132).[67]

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 is required to determine eligibility for selpercatinib. In England, key oncogenic drivers previously used single gene FISH testing or Sanger sequencing, 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.[7, 9] 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.[8]

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.[28]

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, 68] These tests in combination will determine the histology, size, stage and extension of the tumour, which in turn will determine the appropriate treatment strategy.[28] 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.[28, 64]

Confirmation of *RET*-testing is also 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

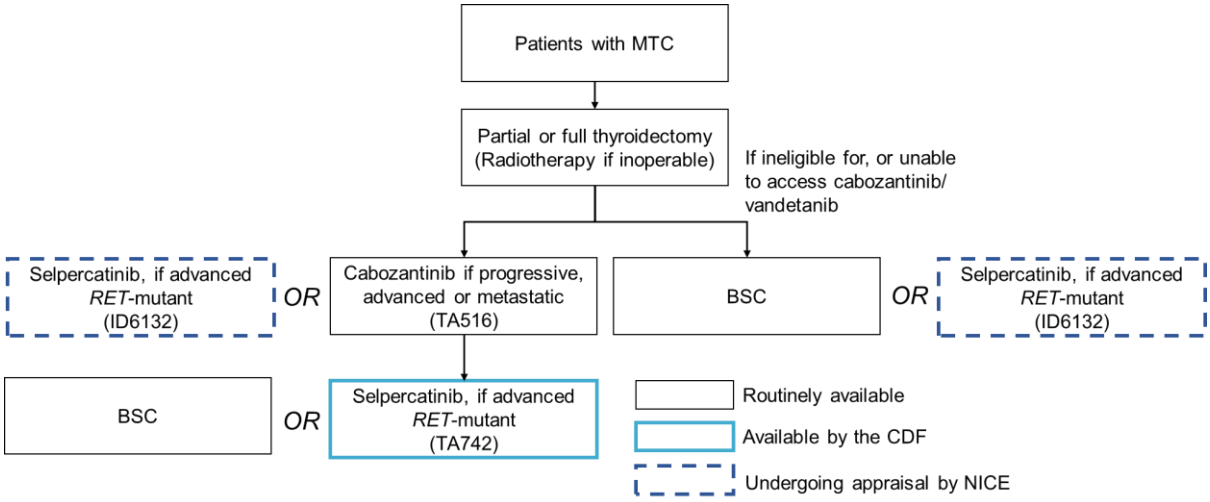
The long-term prognosis for patients with MTC is worse than that of DTC, but still remains favourable if treated effectively. Some patients may survive for many years even with a significant tumour burden, despite the poorer prognosis. This adds extra challenges when making decisions on the risk/benefit for persistent or recurrent disease when considering additional interventions.[38] 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.[28] Furthermore, prophylactic thyroidectomy should be offered to family members with mutations associated with multiple endocrine neoplasia (MEN) syndrome.[28]

Cabozantinib is the only recommended treatment in the UK for progressive, unresectable locally advanced or metastatic MTC in adults (TA516).[26] Following cabozantinib, for those patients' whose disease has progressed and are *RET* mutant-positive, selpercatinib is currently available via the CDF with BSC representing the only other remaining option.[28] Selpercatinib is currently undergoing evaluation as a treatment for patients with systemic therapy naïve advanced *RET*-mutant MTC (ID6132).[67]

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 who have progressed following prior systemic treatment (cabozantinib and/or vandetanib) is outlined in Figure 4. This treatment pathway was validated as representative of UK clinical practice by UK clinical experts during interviews conducted to support ID6132, the ongoing NICE appraisal for selpercatinib in patients with advanced *RET*-altered TC and MTC who have not previously received systemic therapy.[69]

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



Selpercatinib is currently reimbursed via the CDF in the second line setting for MTC (NICE TA742).[3]
Selpercatinib is currently being appraised as part of the ongoing first-line appraisal for *RET*-altered MTC (NICE ID6132).[67]
Abbreviations: BSC: best supportive care; CDF: Cancer Drug's Fund; MTC: medullary thyroid cancer; NICE: National Institute of Health and Care Excellence; *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.[11, 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 NICE TA742.[3]

Survival data for patients with advanced MTC is available from the EXAM trial, with the placebo arm (a proxy for BSC) of the trial including patients with and without prior treatment with systemic therapy. Median OS for the placebo arm of the EXAM trial was 21.1 months. OS was slightly

poorer in the *RET* M918T-positive subgroup treated with placebo, with a median OS of 18.9 months.[54] Furthermore, available data from the EXAM trial indicates that the median PFS in patients with MTC treated with cabozantinib or placebo (including both patients who had, and had not, received prior systemic therapy) was 11.2 months and 4.0 months, respectively.[54] These data indicate that following disease progression with first-line MKIs, survival in patients with advanced MTC is poor. As the trial is comprised of a combination of patients who had and had not received prior systemic treatment, rate of progression and survival is expected to be worse in a previous treated-specific subgroup than these data indicate.

By making selpercatinib routinely available in UK clinical practice, patients with advanced, *RET*-mutant MTC who have progressed on prior systemic therapy will have continued access to an effective treatment as an alternative to BSC. Without selpercatinib as a treatment option for patients with previously treated MTC, survival in this patient population is extremely poor, thus, there is a high unmet need for an active treatment to become routinely available in UK clinical practice. Despite the anticipated recommendation for selpercatinib in patients with advanced *RET*-mutant MTC who have not previously received systemic treatment (ID6132), this unmet need is expected to continue to exist for several years. This is because patients already receiving systemic therapy for their disease (i.e. cabozantinib or vandetanib) will eventually progress and require further treatment.[67] 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 the addition of minimal off-target effects.[11] Therefore, selpercatinib provides a tolerable active treatment option for patients who have experienced disease progression following prior treatment.

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.[28]

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.[28]

Thyroid cancer treatment pathway

As the long-term prognosis for patients treated for DTC is usually favourable when disease is localised, 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.[12, 38, 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.[28] The majority of patients with a tumour more than 1cm in diameter, who have undergone total or near-total thyroidectomy, have I^{131} (radioactive iodine) ablation.[28] Patients who develop local, regional or metastatic disease (5–20% of patients) not amenable to surgery should be treated with radioactive iodine therapy.[28]

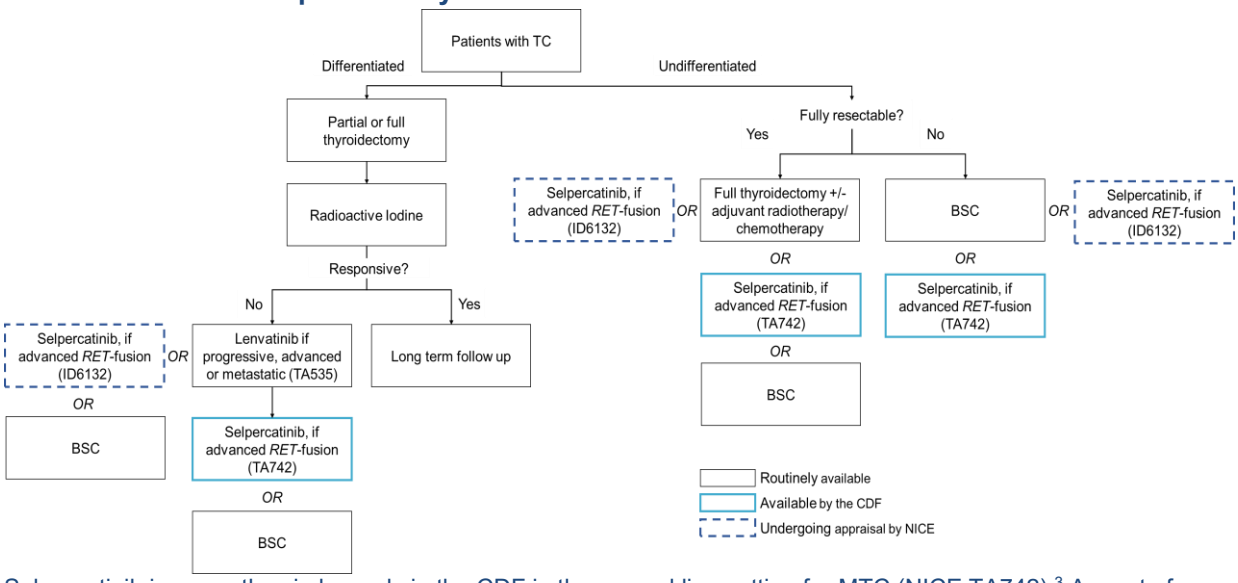
Around 5% to 15% of people with DTC develop radioactive iodine refractory DTC.[70] In the UK, lenvatinib and sorafenib are the only treatments recommended for adult patients with DTC classified as progressive, advanced or metastatic that was not responsive to radioactive iodine, if they are TKI-naïve (TA535).[27] For those patients' whose disease has progressed following first-line lenvatinib and sorafenib, selpercatinib is currently available in UK in a for patients with previously treated TC via the CDF, with BSC representing the only alternative routinely available treatment option.[28] As such, should selpercatinib not become available via routine commissioning, BSC is the only treatment option.

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.[28] As lenvatinib and sorafenib are only recommended for patients with DTC, selpercatinib is currently available via the CDF for adult patients who have *RET* fusion-positive ATC and who have had no prior treatment with a MKI.[71]

There are currently no active treatment options for systemic therapy naïve adolescent patients aged 12–17 years old with TC, so these patients typically receive BSC with some clinicians requesting active treatment through compassionate use.[69]

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 progressed following prior systemic treatment (lenvatinib and/or sorafenib), is outlined in Figure 5. Selpercatinib is currently undergoing evaluation as a treatment for patients with systemic therapy naïve advanced *RET* fusion-positive TC (ID6132). This treatment pathway was validated as representative of UK clinical practice by UK clinical experts interviewed to support the ongoing appraisal for selpercatinib in treatment naïve patients, ID6132.[42]

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



Selpercatinib is currently reimbursed via the CDF in the second line setting for MTC (NICE TA742).[3] As part of TA742, adults with *RET* fusion-positive ATC may receive selpercatinib without prior treatment with lenvatinib and/or sorafenib. Selpercatinib is currently being appraised as part of the ongoing first-line appraisal for MTC (NICE ID6132).[67]

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%.[18] The currently approved first-line MKI treatments, lenvatinib and sorafenib, are associated with a poor prognosis so there is a need for effective treatments for previously treated patients.[3,18, 70] In the Phase III SELECT trial, which assessed the efficacy of lenvatinib for treating progressive, locally advanced or metastatic DTC, a median OS of 34.5 months (95% CI: 21.7, NE) was reported for patients that received placebo (a proxy for BSC). However, in the SELECT trial, no data are reported for a *RET*-fusion positive subgroup and these data include both patients who had and had not received a prior systemic therapy.[55] Therefore, the prognosis for patients with advanced *RET* fusion-positive TC with prior exposure to MKIs, may be worse than these data suggest.

Currently, patients with advanced *RET* fusion-positive TC, who have progressed on first-line therapy, can receive selpercatinib via the CDF. However, without access to selpercatinib as a treatment option, the only alternative option for previously treated patients is palliative treatment with BSC which is associated with a poor prognosis. As such, there is a high unmet need in patients who have received prior systemic therapy for continued access to an effective and tolerable treatment option that is routinely available in UK clinical practice. Despite the anticipated recommendation of selpercatinib for patients with advanced, *RET* fusion-positive TC who are systemic therapy naïve (ID6132), this unmet need will continue to exist for several years. This is because patients already receiving systemic therapy for their disease (i.e. lenvatinib or sorafenib) will eventually progress and require further treatment.[67] Through selective targeting of *RET*-mutations, there is the potential for potent anti-tumour efficacy with minimal off-target effects, allowing selpercatinib to address this unmet need.[11, 72]

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 following prior treatment with cabozantinib and/or vandetanib
- For people aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib and/or sorafenib

For both patients with advanced *RET*-mutant MTC who require systemic therapy after cabozantinib and/or vandetanib, and patients with advanced *RET*-fusion positive TC who require systemic therapy after lenvatinib and/or sorafenib, BSC is the relevant comparator to selpercatinib in this submission. Should selpercatinib no longer be available to patients in this setting, BSC would represent their only option.

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 routinely available to patients who require systematic therapy following prior treatments with MKIs, representing a substantial improvement in care for patients with advanced *RET*-fusion positive TC and *RET*-mutant MTC who would otherwise face an extremely poor prognosis.

With highly specific and potent targeting of *RET* alterations, selpercatinib represents an effective alternative treatment option to BSC. Selpercatinib offers an effective treatment option with a tolerable AE profile for patients with *RET*-altered thyroid cancer who do not respond to or have progressed on prior systemic therapy. As such, selpercatinib should be made routinely available in UK clinical practice to ensure continued access for patients with advanced *RET*-mutant MTC or advanced *RET* fusion-positive TC who have received prior systemic therapy.

B.1.4 *Equality considerations*

Females are more likely to be diagnosed with thyroid cancer than males, with UK data indicating that 72% of thyroid cancer cases occur in females and the remaining 28% in males.[48] Therefore, routine access to selpercatinib for the treatment of thyroid cancer in patients who have received prior systemic therapy 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 following prior systemic treatment

LIBRETTO-001

- The clinical evidence base for selpercatinib in patients with advanced *RET*-altered TC and MTC is provided by the most recent data cut off (DCO) of the LIBRETTO-001 trial, the 13th January 2023 DCO: this trial is an ongoing, multicentre, Phase I/II, open-label study that enrolled 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 had received prior cabozantinib/vandetanib (N=152) and a cohort of patients with *RET*-fusion positive TC who had received prior systemic therapy (N=41).
    - Due to comparator data availability, data from the any-line MTC (N=295) and TC (N=65) patient populations are used in the indirect treatment comparisons (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 advanced *RET* fusion-positive TC and *RET*-mutant MTC who require systemic therapy and whose disease has progressed after prior systemic therapy in UK clinical practice.

Efficacy

- The primary endpoint in the LIBRETTO-001 trial was objective response rate (ORR). ORR in the prior cabozantinib/vandetanib *RET*-mutant MTC population was 77.6% (118/152; 95% confidence interval [CI]: 70.2, 84.0), and in the prior systemic therapy *RET* fusion-positive TC population, ORR was 85.4% (35/41; 95% CI: 70.8, 94.4).[73]
    - The majority of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population experienced at least a partial response (PR) following treatment with selpercatinib, with 65.1% of patients experiencing a PR and 12.5% of patients experiencing a complete response (CR).[73]
    - The majority of patients (73.2%) in the prior systemic therapy *RET* fusion-positive TC population experienced a PR, and 12.2% patients experienced a CR, following treatment with selpercatinib.[73]
- In the prior cabozantinib/vandetanib *RET*-mutant MTC population, median duration of response (DOR) was 45.3 months and median progression-free survival (PFS) was 41.4 months, with median follow-up of 38.3 months and 44.0 months, respectively.[73] While median OS was reached in this patient population, this result was not considered meaningful due to the shorter median duration of follow up (46.9 months).
- In the prior systemic therapy *RET* fusion-positive TC population median DOR was 26.7 months, median PFS was 27.4 months and median OS was not reached, with a median follow-up of 33.9 months, 30.4 months, and 36.9 months, respectively.[73, 74]
- Overall, results observed in the prior cabozantinib/vandetanib *RET*-mutant MTC (N=152) and the prior systemic therapy *RET* fusion-positive TC (N=41) populations were promising. Results observed in the any-line MTC (N=295) and TC (N=65) populations were consistent with results observed in the prior systemic treatment-specific MTC and TC populations.
- Efficacy data from the Systemic Anti-Cancer Therapy (SACT) dataset are also available for the *RET*-mutant MTC patient population only, and are provided in the reference pack alongside this submission for completeness.[75] Due to the immaturity of these data and the small sample size, these data were not deemed suitable to inform efficacy estimates in this submission.

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 the relevant comparator in the TC and MTC indications. Therefore, ITCs were conducted to inform the relative efficacy estimates for selpercatinib in LIBRETTO-001 versus the relevant comparator for this appraisal.
    - For selpercatinib versus BSC in the *RET*-mutant MTC population, matching adjusted indirect comparison (MAICs) were conducted.
    - For selpercatinib versus BSC in the *RET* fusion-positive TC population, naïve ITCs were conducted.
- Overall, the ITCs conducted to generate comparative efficacy evidence for selpercatinib versus BSC used the best available data and methods outlined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[76] In both the *RET*-mutant MTC and *RET* fusion-positive TC populations, selpercatinib demonstrates clinically meaningful and statistically significant treatment benefits, in terms of PFS and OS, versus BSC, the relevant comparator 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.[73]
- 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.[73]
- Grade 3 or 4 TEAEs were reported in 249 (76.9%) patients in the RET-mutant MTC SAS and 47 (71.2%) patients in the *RET* fusion-positive TC SAS, irrespective of relatedness to selpercatinib.[74]
- 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 advanced *RET*-altered TC and MTC who have received prior systemic therapy versus BSC. Safety evidence from the LIBRETTO-001 trial also demonstrates that selpercatinib is a well-tolerated active treatment.
- As such, selpercatinib offers a tolerable and effective treatment option, driving a deep and durable response in patients, who would otherwise 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, ongoing 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 conditional marketing authorisation in adults with *RET* fusion-positive TC who had previously received prior lenvatinib or sorafenib. As discussed in Section B.1.1, this trial is also being used to support the anticipated marketing authorisation expansion to include people aged 12 years and older with RET fusion-positive TC (for both lenvatinib/sorafenib naïve and experienced patients).

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.[77] 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:

- People aged 12 years and over with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib
- People aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib and/or sorafenib

Table 3: Clinical effectiveness evidence

Study	**LIBRETTO-001 (NCT03157128)[77, 78]**
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:[a] • 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 Lansky performance score (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 twice daily (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	N/A		
Reported outcomes specified in the decision problem	**Measures of disease severity and symptom control:**[b] • 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] These represent generic inclusion criteria for all patients in the LIBRETTO-001 trial. 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. The 'no standard therapy exists' criteria applies only to patients with tissue agnostic solid tumours. [b] 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)[78]

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 (patients with tissue agnostic solid tumours only), 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.[77, 78]

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.[77, 78] 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 BID.[79] 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).

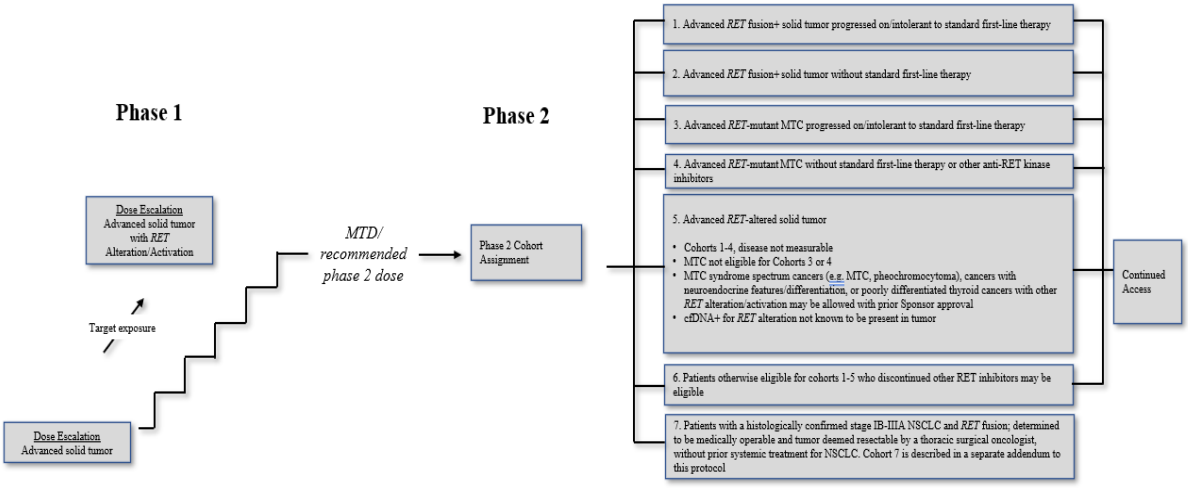
Table 4: LIBRETTO-001 patient cohorts

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)[78]

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)[78]

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 following prior cabozantinib or vandetanib, corresponding to 'MTC:Cab/Van': the prior cabozantinib/vandetanib *RET*-mutant MTC population (N=152)
- People aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy following prior lenvatinib or sorafenib, corresponding to 'TC:TrtSys': the prior systemic therapy *RET* fusion-positive TC population (N=41)

As LIBRETTO-001 is a single-arm trial, the clinical effectiveness and safety of selpercatinib in *RET*-altered TC and MTC versus BSC in UK clinical practice could not be assessed directly.

Thus, 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 analysis sets:

- MTC any-line population (N=295): comprised of the 'MTC: Cab/Van Naïve' population (N=143) and the 'MTC: Cab/Van' population (N=152)
- TC efficacy any-line (N=65): comprised of the 'TC: TrtSysNaïve' population (N=24) and the 'TC: TrtSys' population (N=41)

For completeness, clinical effectiveness results for these populations 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) 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).[78]

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 patient populations.
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[b] 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 patient populations.
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[c] 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. [b] Throughout this submission, the MTC:Cab/Van population is referred to as the prior cabozantinib/vandetanib *RET*-mutant MTC population. [c] Throughout this submission, the TC:TrtSys population is referred to as the prior systemic therapy *RET* fusion-positive TC population.
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).[78]

Available data cut-offs

The efficacy and safety evidence for selpercatinib presented in this submission is informed by the most recent data cut for *RET*-altered TC and MTC in the LIBRETTO-001 trial: the 13th January 2023 DCO. Data from two prior DCOs (16th December 2019 and 15th June 2021), which represent the main data cuts for the MTC and TC populations, are presented in Appendix M.3.

Enrolment into the LIBRETTO-001 trial ended on 1st February 2024; enrolment of the prior cabozantinib/vandetanib *RET*-mutant MTC population ended on 7th June 2019, and enrolment of the prior systemic therapy *RET* fusion-positive TC ended on 1st July 2022. Although the LIBRETTO-001 trial is still ongoing, [redacted].

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.[78] 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)
	  ○ Red blood cell 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 proton pump inhibitors (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 independent review committee (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 prior cabozantinib/vandetanib *RET*-mutant MTC and prior systemic therapy *RET* fusion-positive TC populations (see Table 5, Section B.2.4 for definitions of these populations):
	• 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 46.9 months and 36.9 months 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; 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)[78], Wirth *et al* (2024).[74]

B.2.3.2 Patient characteristics

A summary of patient demographics, along with other baseline characteristics, is provided below for the prior cabozantinib/vandetanib *RET*-mutant MTC patient population (N=152) and the any-line *RET*-mutant MTC patient population (N=295), along with the prior systemic therapy *RET* fusion-positive TC patient population (N=41) and the any-line *RET* fusion-positive TC population (N=65).

RET-mutant medullary thyroid cancer

The baseline demographics and disease characteristics of the prior cabozantinib/vandetanib *RET*-mutant MTC population (N=152) and the any-line *RET*-mutant MTC population (N=295) in the LIBRETTO-001 trial are presented in Table 7. A summary of prior cancer-related treatments for the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population enrolled in the LIBRETTO-001 trial is also provided in Table 8.

The median age of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population was 58.0 years, with a wide range of patient ages (17–90 years). The prior cabozantinib/vandetanib *RET*-mutant MTC population included more males (63.8%) than females (36.2%) and the majority of the population were White (90.1%).[73]

For the prior cabozantinib/vandetanib *RET*-mutant MTC population (N=152), the median time from diagnosis at the 13th January 2023 DCO was [redacted] months; the majority of patients (92.8%) 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.

In the prior cabozantinib/vandetanib *RET*-mutant MTC patient population, all patients had received prior MKIs. Overall, 83 (54.6%) patients had previously received cabozantinib and 120 (78.9%) patients had received vandetanib, with [redacted] ([redacted]) patients previously receiving both cabozantinib and vandetanib. Furthermore, nine (5.9%) patients had received sorafenib and 15 (9.9%) patients had received lenvatinib.[73, 74] Additionally, 16 (10.5%) patients had received 'other' types of systemic therapy, including radioactive iodine and mammalian target of rapamycin (mTOR) inhibitors.[74]

As shown by Table 7, baseline characteristics of the MTC any-line population were closely aligned with characteristics of the prior cabozantinib/vandetanib *RET*-mutant MTC population. Due to the difference in criteria for prior cancer treatments in the populations comprising the any-line and the prior cabozantinib/vandetanib *RET*-mutant MTC populations, prior systemic treatments between the two patient populations 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 prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population[a] N=295
Age, years		
Median	58.0	58.0
Mean	[redacted]	[redacted]
Range	17–90	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	97 (63.8)	180 (61.0)
Female	55 (36.2)	115 (39.0)
Race, n (%)		
White	137 (90.1)	261 (88.5)
Black or African American	2 (1.3)	4 (1.4)
Asian	2 (1.3)	10 (3.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)
American Indian or Alaska Native	1 (0.7)	1 (0.3)
Other	10 (6.6)	17 (5.8)
Missing	0 (0.0)	1 (0.3)
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	42 (27.6)	111 (37.6)
1	99 (65.1)	167 (56.6)
2	11 (7.2)	17 (5.8)
Stage at entry, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]

IV	141 (92.8)	[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	11 (7.2)	14 (4.7)

[a] The MTC any-line population includes the MTC: Cab/VanNaïve and MTC: Cab/Van populations. [b] [redacted] in the prior cabozantinib/vandetanib *RET*-mutant MTC population and [redacted] in the any-line *RET*-mutant MTC population 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 population; n: number of patients; RET: rearranged during transfection; Van: vandetanib.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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

	***RET*-mutant MTC prior cabozantinib/vandetanib N=152**	***RET*-mutant MTC any-line population[a] N=295**
Received prior systemic therapy, n (%)		
Yes	152 (100.0)	179 (60.7)
No	0 (0.0)	116 (39.3)
Type of prior systemic therapy, n (%)		
MKI	152 (100.0)	161 (54.6)
Cabozantinib	83 (54.6)	83 (28.1)
Vandetanib	120 (78.9)	120 (40.7)

Both cabozantinib and vandetanib	[redacted]	[redacted]
Sorafenib	9 (5.9)	13 (4.4)
Lenvatinib	15 (9.9)	18 (6.1)
Other MKIs	21 (13.8)	23 (7.8)
Other	16 (10.5)	25 (8.5)
Radioactive iodine	0 (0.0)	2 (0.7)
mTOR inhibitor	4 (2.6)	5 (1.7)
VEGF/VEGFR inhibitor	1 (0.7)	0 (0.0)
Selective *RET* inhibitor	1 (0.7)	1 (0.3)
Hormonal therapy	0 (0.0)	1 (0.3)
Other systemic therapy	12 (7.9)	2 (0.7)
Number of prior systemic regimens, n (%)		
0	[redacted]	116 (39.3)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	42 (27.6)	[redacted]
Prior systemic regimens		
Median	2.0	[redacted]
Range	1–8	[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 populations.
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 population; 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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

RET fusion-positive thyroid cancer

The baseline demographics and the disease characteristics of the prior systemic therapy *RET* fusion-positive TC (N=41) and the any-line *RET* fusion-positive TC (N=65) patient populations 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.

Of the 41 patients in the prior systemic therapy *RET*-fusion positive TC population, 35 (85.4%) had previously received MKIs. The majority of patients had previously received lenvatinib (N=26; 63.4%) and nine patients had previously received sorafenib (N=9; 22.0%); thus, [redacted] ([redacted]) patients in this population had received a prior treatment regimen specified in the original NICE guidance for selpercatinib in this indication (TA742).[3] Of these patients, [redacted]([redacted]) patients had received both lenvatinib and sorafenib. Additionally, one patient had previously received cabozantinib (N=1; 2.4%) and one patient had previously received vandetanib (N=1; 2.4%).

The prior systemic therapy *RET* fusion-positive TC population included four different thyroid histological subtypes; the majority of patients were diagnosed with papillary TC (N=31; 75.6%), with five cases of poorly differentiated TC (N=5; 12.2%), four cases of anaplastic TC (N=4; 9.8%) and one case of Hürthle cell TC (N=1; 2.4%) observed.

Median age for the prior systemic therapy *RET* fusion-positive TC population was 58.0 years, also featuring a wide age range of 25–88 years. There were more females (56.1%) than males (43.9%) in the patient population, and the majority of patients (58.5%) were White.[73]

The median time from initial diagnosis was [redacted] months for the prior systemic therapy *RET* fusion-positive TC population. [redacted] had metastatic disease at enrolment, with a median time since diagnosis of metastatic disease of [redacted] months. The majority of patients had Stage IV disease at entry to the study (87.8%). Of the prior systemic therapy *RET*-fusion positive TC patients, 30 out of 41 (73.2%) patients had received systemic radioactive iodine as a prior therapy. By definition, all patients in the prior systemic therapy *RET*-fusion positive TC population had received a prior systemic therapy other than radioactive iodine.

Baseline demographic characteristics were broadly aligned between the any-line *RET* fusion-positive TC population and the prior systemic therapy *RET* fusion-positive TC population. Due to the differences in criteria between the prior systemic therapy and the any-line *RET*-fusion positive TC populations, the prior systemic treatments received by patients in these populations varied, 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 prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] N=65
Age, years		
Median	58.0	59.0
Mean	[redacted]	[redacted]
Range	25–88	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	18 (43.9)	32 (49.2)

Female	23 (56.1)	33 (50.8)
Race, n (%)		
White	24 (58.5)	42 (64.6)
Black	3 (7.3)	3 (4.6)
Asian	12 (29.3)	13 (20.0)
Other	2 (4.9)	5 (7.7)
Missing	0 (0.0)	2 (3.1)
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	11 (26.8)	25 (38.5)
1	27 (65.9)	36 (55.4)
2	3 (7.3)	4 (6.2)
Smoking history, n (%)		
Never smoked	28 (68.3)	40 (61.5)
Former smoker	13 (31.7)	23 (35.4)
Current smoker	0 (0.0)	1 (1.5)
Missing	0 (0.0)	1 (1.5)

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; N: number of patients in population; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[78] Wirth *et al* (2023)[73], Raez *et al* (2023),[80] Wirth *et al* (2024).[74]

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

Characteristic	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] N=65
Primary tumour type, n (%)		
Papillary thyroid	31 (75.6)	54 (83.1)

Poorly differentiated thyroid	5 (12.2)	6 (9.2)
Anaplastic thyroid	4 (9.8)	4 (6.2)
Hürthle cell thyroid	1 (2.4)	1 (1.5)
Stage at entry, n (%)		
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	36 (87.8)	[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	12 (29.3)	13 (20.0)

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys population.
Abbreviations: CNS: central nervous system; N: number of patients in population; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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

	***RET* fusion-positive TC prior systemic therapy N=41**	***RET* fusion-positive TC any-line population[a] N=65**
Received prior systemic therapy, n (%)		
Yes	41.0 (100.0)	53 (81.5)
Type of prior systemic therapy, n (%)		
MKI	35 (85.4)	35 (53.8)
Cabozantinib	1 (2.4)	1 (1.5)
Vandetanib	1 (2.4)	1 (1.5)
Sorafenib	9 (22.0)	9 (13.8)
Lenvatinib	26 (63.4)	26 (40.0)
Other MKIs	7 (17.1)	7 (10.8)
Chemotherapy	8 (19.5)	8 (12.3)

Platinum	4 (9.8)	4 (6.2)
Taxane	5 (12.2)	5 (7.7)
Immunotherapy	3 (7.3)	3 (4.6)
Other	30 (73.2)	48 (73.8)
mTOR inhibitor	2 (4.9)	2 (3.1)
EGFR inhibitor	1 (2.4)	1 (1.5)
Radioactive iodine therapy	30 (73.2)	48 (73.8)
Other systemic therapy	4 (9.8)	4 (6.2)
Number of prior systemic regimens, n (%)		
0	0 (0.0)	6 (9.2)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Prior systemic regimens		
Median	3.0	[redacted]
Range	1–7	[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 prior systemic therapy *RET* fusion-positive TC population includes patients who had previously received systemic therapy, in addition to radioactive iodine (if received). [b] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations.
Abbreviations: EGFR: Epidermal growth factor receptor**;** MKI: multi-kinase inhibitor; mTOR: mammalian target of rapamycin; N: number of patients in population; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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 prior cabozantinib/vandetanib and the any-line *RET*-mutant 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 prior systemic therapy and the any-line *RET*-fusion positive TC patient populations are provided in Table 14.

The most common *RET* alteration in the prior cabozantinib/vandetanib *RET*-mutant MTC population was the M918T mutation, occurring in 99 (65.1%) patients. Similarly, this was the most common mutation observed in the any-line MTC population (in 62.7% of patients).[74] In the prior cabozantinib/vandetanib *RET*-mutant 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 prior systemic therapy *RET* fusion-positive TC population was the CCDC6 fusion, occurring in 25 (61.0%) of patients. Similarly, this was the most frequently observed mutation in the any-line *RET* fusion-positive TC population (in 61.5% of patients).[74] The most frequently used assay to detect *RET* alterations in this patient population was 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 populations, 13th January 2023 DCO)

Status	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
RET mutation type, n (%)		
M918T	99 (65.1)	185 (62.7)
V804 M/L	8 (5.3)	14 (4.7)
Extracellular Cysteine Mutation	24 (15.8)	58 (19.2)
Other	21 (13.8)	38 (12.9)
***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] The MTC any-line population includes the MTC: Cab/VanNaïve and the MTC: Cab/Van populations.
Abbreviations: Cab: cabozantinib; CSR: clinical study report; DCO: data cut-off; PCR: polymerase chain reaction; MTC: medullary thyroid cancer; N: number of patients in population; 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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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

Status	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] N=65
***RET* fusion type (n, %)**		
CCDC6	25 (61.0)	40 (61.5)
NCOA4	8 (19.5)	15 (23.1)
Other	7 (17.1)	9 (13.8)
Unknown	1 (2.4)	1 (1.5)
***RET* alteration, type of assay (n, %)**		
NGS on tumour	[redacted]	[redacted]
NGS on blood or plasma	[redacted]	[redacted]
FISH	[redacted]	[redacted]
Other	[redacted]	[redacted]

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations.
Abbreviations: DCO: data cut-off; FISH: fluorescence in situ hybridisation; PCR: polymerase chain reaction; MTC: medullary thyroid cancer; N: number of patients in population; 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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

B.2.3.4 Patient disposition

RET-mutant medullary thyroid cancer

A summary of the patient disposition of the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population is provided in Table 15, with patient disposition across the populations illustrated by the CONSORT diagram in Figure 8.

Of the 152 patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population, [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 this population stayed on treatment post-progression as of 13th January 2023.

A lower proportion of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population 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 broadly aligned between the populations.

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

[a] The MTC population includes the MTC:Cab/VanNaive, the MTC:Cab/Van, and the MTC:NMD populations.
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).[78]

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

	***RET*-mutant MTC prior cabozantinib/vandetanib N=152**	***RET*-mutant MTC efficacy analysis set[a] N=295**
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] The MTC any-line population includes the MTC: Cab/VanNaïve and the MTC: Cab/Van populations.
Abbreviations: MTC: medullary thyroid cancer; N: number of patients in population; n: number of patients; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[78]

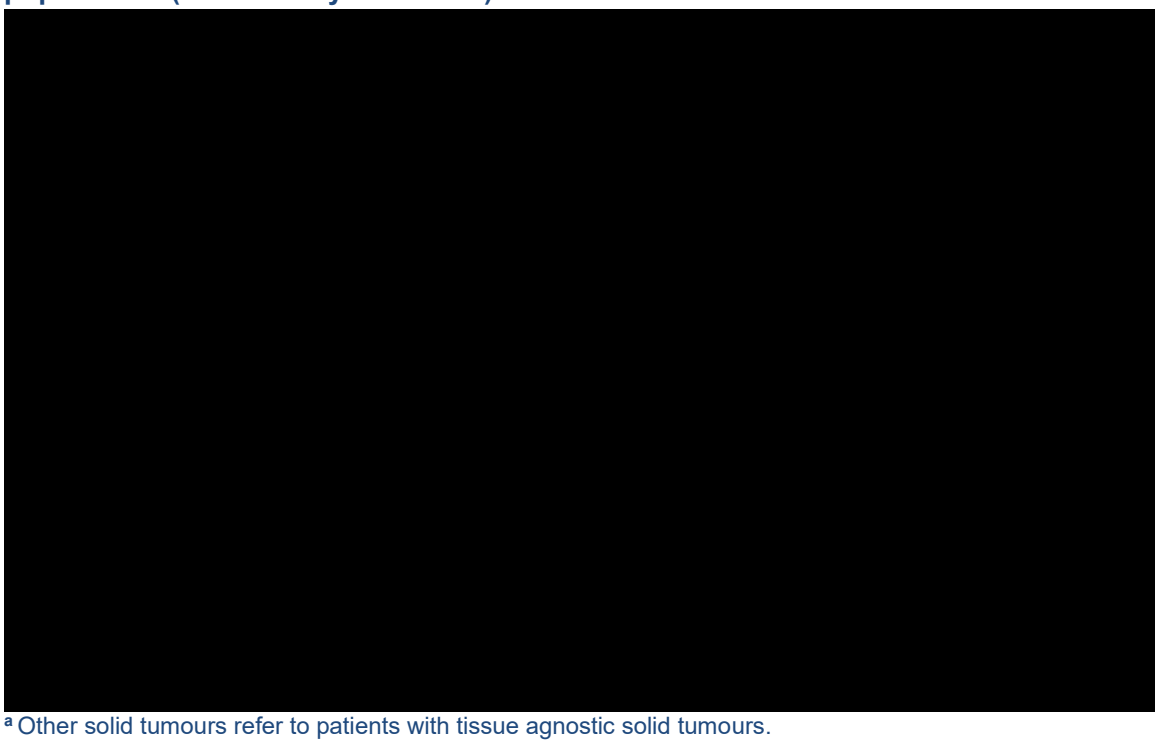
RET fusion-positive thyroid cancer

A summary of the patient disposition for the prior systemic therapy *RET* fusion-positive population and the any-line *RET* fusion-positive TC population in the LIBRETTO-001 trial is provided in Table 16, with patient disposition across these populations also illustrated in Figure 9.

Of the 41 patients in the prior systemic therapy *RET*-fusion positive TC population, [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 this population stayed on treatment post-progression as of 13th January 2023; [redacted] of these [redacted] patients remained on treatment with selpercatinib. Additionally, [redacted] occurred in this patient population.

Similarly to the trends observed between the MTC populations, the prior systemic therapy *RET* fusion-positive TC population had a lower 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 populations (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).[78]

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

	RET fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] 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] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations. [c] [redacted] patients continued treatment post-progression in the prior systemic therapy *RET* fusion-positive TC population; at the 13th January 2023 DCO, [redacted] patients were still continuing treatment.
Abbreviations: N: number of patients in population; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[78]

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 most recent 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. Only the 16th December 2019 DCO was available to inform the efficacy and safety of selpercatinib in the original appraisal in this indication, TA742.[3] As such, this CDF exit submission is informed by clinical data with substantially increased median duration of follow-up and increased patient numbers compared with the original appraisal in this indication (TA742). This is particularly relevant for the TC population, for which the number of patients in the prior systemic therapy *RET* fusion-positive TC population increased from 19 to 41 patients between the 19th December 2019 and the 13th January 2023 DCOs.

For completeness, top-line clinical efficacy results are presented for the 16th December 2019 and 15th June 2021 DCOs in Appendix M.3. Although enrolment into the LIBRETTO-001 trial has now ended, the LIBRETTO-001 is currently still ongoing. [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 M.1 • 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 dose limiting toxicity (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).[78]

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of selpercatinib for patients with *RET*-altered TC and MTC who had previously received systemic therapy. Definitions for these outcome measures are presented in Table 18.

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

Outcome measure	Definition
Primary outcome	
Objective response rate	ORR was defined as the proportion of patients with BOR of confirmed CR or confirmed PR based on RECIST v1.1. 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:[81] • **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.[82] 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 patients with *RET*-mutant MTC who received prior cabozantinib/vandetanib and for patients with *RET* fusion-positive TC who received prior systemic therapy for the 13th January 2023 DCO.

Abbreviations: BOR: best overall response; CR: complete response; DCO: data cut-off; DOR: duration of response; EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumours, version 1.1.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[78]

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.[83]	
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.[84]	
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[85]	
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).[78]	
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 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 44.6 months and 38.7 months for the MTC and the TC patient populations of relevance to this submission, respectively.[74] 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.

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 13th 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 available via routine commissioning for patients with *RET*-altered tumours in the second-line; selpercatinib is currently available through the CDF.[3]
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: multi-kinase 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 [redacted] DCO (13th January 2023) for the TC and MTC populations in the LIBRETTO-001 trial, unless otherwise stated. Results are presented for the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population, and the prior systemic therapy *RET* fusion-positive TC population and the any-line TC *RET* fusion-positive population.
    - In the prior cabozantinib/vandetanib *RET*-mutant MTC population, median duration of follow-up for DOR was 38.3 months. In the prior systemic therapy *RET* fusion-positive TC population, median duration of follow-up for DOR was 33.9 months.

RET-mutant medullary thyroid cancer

- The primary endpoint in the LIBRETTO-001 trial, ORR, in the prior cabozantinib/vandetanib *RET*-mutant MTC population was 77.6% (118/152; 95% CI: 70.2, 84.0).[73]
    - 65.1% of patients experienced a PR following treatment with selpercatinib, along with 12.5% of patients experiencing a CR, demonstrating the efficacy in targeting *RET* in this patient population.[73]
- Key secondary outcomes also assessed in LIBRETTO-001 included DOR and PFS by IRC assessment, and OS.
    - With a median follow-up of 38.3 months, median DOR was 45.3 months (95% CI: 33.6, NE) in the prior cabozantinib/vandetanib *RET*-mutant MTC population; disease progression was observed in [redacted] responding patients.[73]
    - With a median follow-up of 44.0 months, median PFS (IRC) was 41.4 months (95% CI: 30.2, NE) in the prior cabozantinib/vandetanib *RET*-mutant MTC population with 53 (34.9%) progression events at the DCO. At the time of the DCO, [redacted] patients were alive without documented disease progression (PD).[73, 74]
    - At ≥36 months, a survival rate of 67.8% (95% CI: 59.4, 74.8) was observed for the prior cabozantinib/vandetanib *RET*-mutant MTC patient population. At the DCO, [redacted]) patients were still alive. Median OS has been reached in this population but is not considered an informative result due to the shorter median duration of follow-up (46.9 months).[74]
- Efficacy outcomes for the any-line MTC population were consistent with those for the prior cabozantinib/vandetanib *RET*-mutant MTC patient population.

RET fusion-positive thyroid cancer

- ORR in the prior systemic therapy *RET* fusion-positive TC population was 85.4% (35/41; 95% CI: 70.8, 94.4), with 73.2% and 12.2% of patients experiencing PR and CR, respectively. Similarly high rates of efficacy as the prior cabozantinib/vandetanib *RET*-mutant MTC population were therefore reflected in the prior systemic therapy *RET* fusion-positive TC population.[73]
- Key secondary outcomes for the prior systemic therapy *RET* fusion-positive TC population followed broadly similar trends to the prior cabozantinib/vandetanib *RET*-mutant MTC population.
    - With a median follow-up of 33.9 months, median DOR was 26.7 months (95% CI: 12.1, NE). Disease progression was observed in [redacted] responding patients.[73]
    - With a median follow-up of 30.4 months, median PFS was 27.4 months (95% CI: 14.5, NE), with [redacted] progression events observed by IRC assessment at the time of the DCO. [redacted] patients were alive without documented PD at this point.[73]
    - With a median follow-up of 36.9 months, median OS was not reached (95% CI: 25.3, NE). [redacted] patients were alive at the DCO, with a survival rate of 65.5% (95% CI: 46.0, 79.4) reported at ≥36 months.
- Efficacy outcomes for the any-line *RET* fusion-positive TC population were consistent with

those for the prior systemic therapy *RET* fusion-positive TC patient population.

The results presented in this submission are based on the 13th January 2023 DCO, unless noted otherwise. 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 M.1.

An overview of efficacy data from key previous data cuts of LIBRETTO-001 are provided in Appendix M.1. The efficacy data informing this submission show increased maturity and greater numbers of patients within each analysis set when compared with the 16th December 2019 DCO which informed the original NICE appraisal for selpercatinib in this indication (TA742).[3] For example, median PFS in the prior cabozantinib/vandetanib *RET*-mutant MTC population at the 16th December 2019 DCO was NE (95% CI: 24.4, NE) compared with 41.4 months (95% CI: 30.2, NE) in this submission. Furthermore, median duration of follow-up or PFS was 11.7 months at the 16th December 2019 DCO compared with 44.0 months in this submission for the prior cabozantinib/vandetanib *RET*-mutant MTC population.

Results from the populations of relevance to the decision problem, the prior cabozantinib/vandetanib *RET*-mutant MTC population and the prior systemic therapy *RET* fusion-positive TC patient population, are presented in the following sections. For completeness, results for the any-line *RET*-altered TC and MTC 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 recruitment for the *RET*-mutant MTC indication closing before recruitment for the *RET* fusion-positive TC indication. Recruitment closed on 3rd February 2020 for the cabozantinib/vandetanib naïve *RET*-mutant MTC population, 7th June 2019 for the prior cabozantinib/vandetanib *RET*-mutant MTC population and 1st July 2022 for the *RET* fusion-positive TC populations.

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 prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are presented in Table 20. For patients with *RET*-mutant MTC who had received prior cabozantinib/vandetanib, ORR was 77.6% (118/152, 95% CI: 70.2, 84.0), with 19 (12.5%) of patients achieving CR and 99 (65.1%) patients achieving PR. CBR and DCR were high in the prior cabozantinib/vandetanib *RET*-mutant MTC population, with rates of 91.4% (95% CI: 85.8, 95.4) and 94.1% [redacted], respectively. BOR and ORR results for the any-line

MTC population were consistent with the prior cabozantinib/vandetanib *RET*-mutant MTC population.[73, 74]

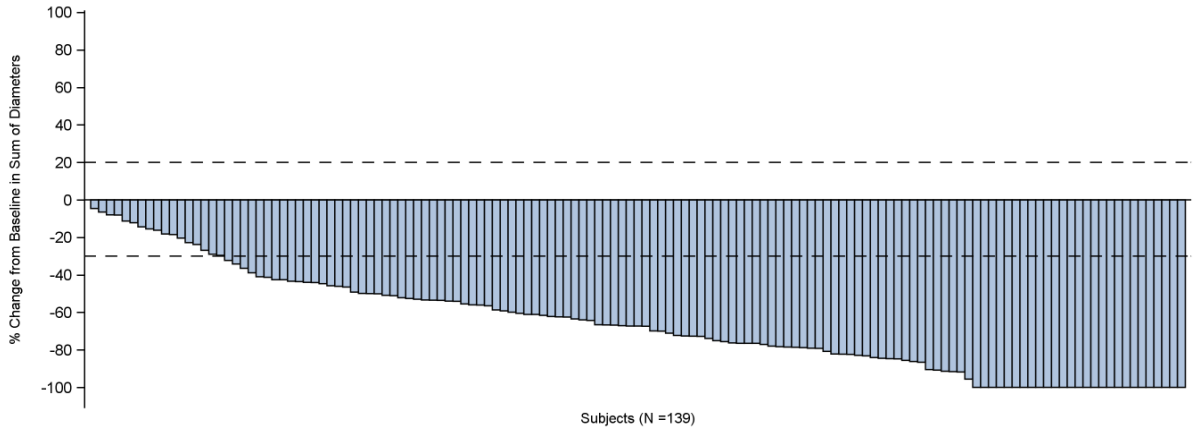
Waterfall plots illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment for the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are shown below in Figure 10 and Figure 11, respectively, indicating that tumours were reduced by >25% for the majority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

Table 20: BOR and ORR based on IRC assessment for the prior cabozantinib/vandetanib and any-line *RET*-mutant MTC populations in the LIBRETTO-001 trial

	***RET*-mutant MTC prior cabozantinib/vandetanib N=152**	***RET*-mutant MTC any-line population N=295**
ORR[a]		
n (%)	118 (77.6)	236 (80.0)
95% CI	(70.2, 84.0)	[redacted]
BOR, n (%)		
CR	19 (12.5)	53 (18.0)
PR	99 (65.1)	183 (62.0)
SD	25 (16.4)	45 (15.3)
SD16+[b]	[redacted]	[redacted]
PD	2 (1.3)	4 (1.4)
Not evaluable	7 (4.6)	10 (3.4)
CBR (CR + PR + SD16+[b])[c]		
n (%)	139 (91.4)	274 (92.9)
95% CI	(85.8, 95.4)	[redacted]
DCR (CR + PR + SD)[d]		
n, (%)	143 (94.1)	281 (95.3)
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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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

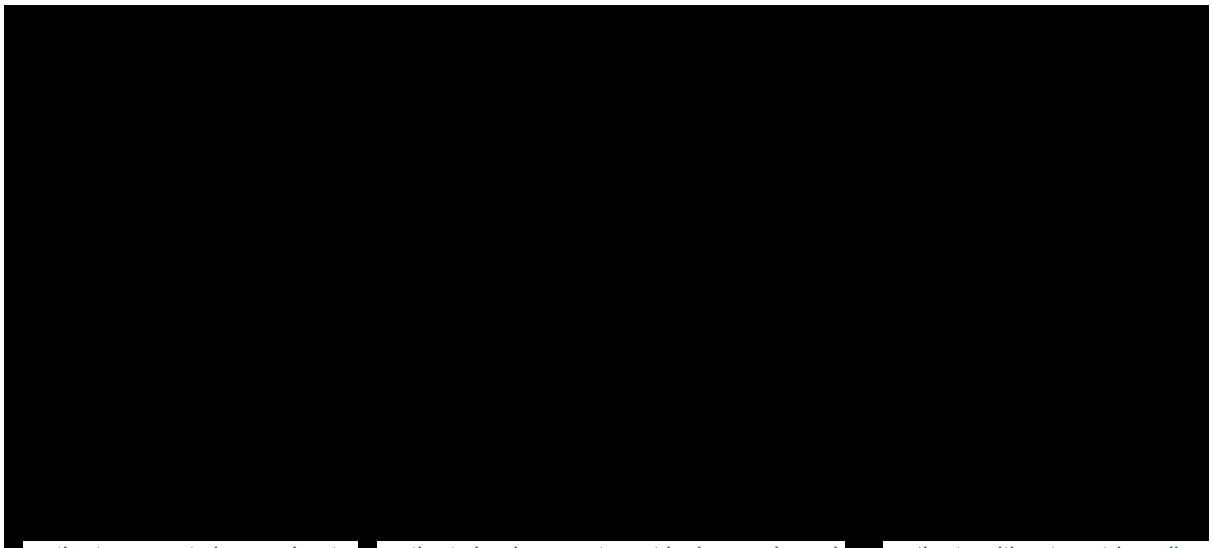


13 patients are not shown, due to seven patients having non-target lesions only and six patients without postbaseline target lesion measurement.

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),[78] Wirth *et al* (2023).[73]

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



[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).[78]

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 prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are summarised in Table 21. For the prior cabozantinib/vandetanib *RET*-mutant MTC population,

after a median follow-up of 38.3 months, the median DOR by IRC was 45.3 months (95% CI: 33.6, NE). In contrast, at the 16th December 2019 DCO informing TA742, the median DOR in this patient population was NE (95% CI: 19.1, NE). Durable response rates in the prior cabozantinib/vandetanib *RET*-mutant MTC population were also observed; 83.0% (95% CI: 74.6, 88.8) of patients were in response for ≥12 months, reaching 60.3% (95% CI: 49.8, 69.3) at ≥36 months.[74] DOR results for the any-line MTC population were broadly consistent with the prior cabozantinib/vandetanib *RET*-mutant MTC population.[73]

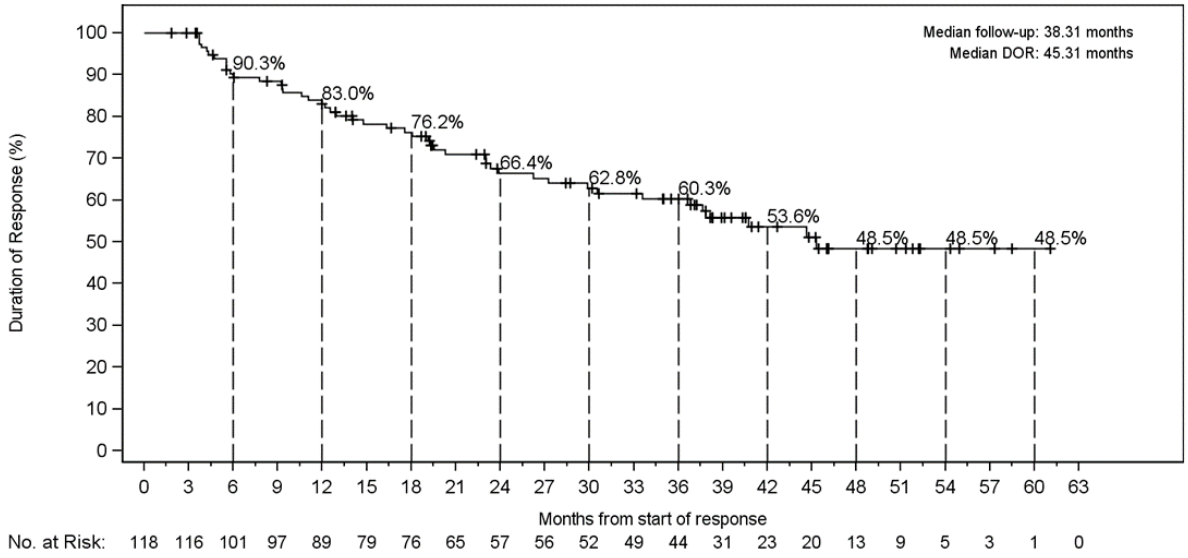
A Kaplan–Meier (KM) plot of DOR for the prior cabozantinib/vandetanib *RET*-mutant MTC population is presented in Figure 12.

Table 21: DOR based on IRC assessment for the prior cabozantinib/vandetanib MTC and the any-line *RET*-mutant MTC populations in the LIBRETTO-001 trial

	***RET*-mutant MTC prior cabozantinib/vandetanib N=152**	***RET*-mutant MTC any-line population N=295**
Responders (n)	118	236
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	45.3	[redacted]
95% CI	33.6, NE	[redacted]
Rate (%) of DOR		
≥12 months (95% CI)	83.0 (74.6, 88.8)	[redacted]
≥24 months (95% CI)	66.4 (56.3, 74.7)	[redacted]
≥36 months (95% CI)	60.3 (49.8, 69.3)	[redacted]
DOR follow-up (months)		
Median	38.3	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	23.0, 46.1	[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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

Figure 12: KM plot of DOR based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population



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: Wirth *et al* (2024).[74]

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 prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are provided in Table 22. For the prior cabozantinib/vandetanib *RET*-mutant MTC population, after a median duration of follow-up of 44.0 months, median PFS was 41.4 months (95% CI: 30.2, NE).[73] At the DCO, [redacted] in this efficacy set were alive without documented disease progression by IRC assessment. The second most common reason for censoring in the prior cabozantinib/vandetanib *RET*-mutant MTC population was subsequent anti-cancer therapy or surgery without documented PD [redacted]. Rates of PFS ranged from 79.5% (95% CI: 71.8, 85.3) for ≥12 months, to [redacted] at ≥36 months for the prior cabozantinib/vandetanib *RET*-mutant MTC population.

PFS results for the any-line *RET*-mutant MTC population were broadly consistent with the prior cabozantinib/vandetanib *RET*-mutant MTC population, with PFS landmark rates for the any-line population being slightly higher than the prior cabozantinib/vandetanib *RET*-mutant MTC population.[73]

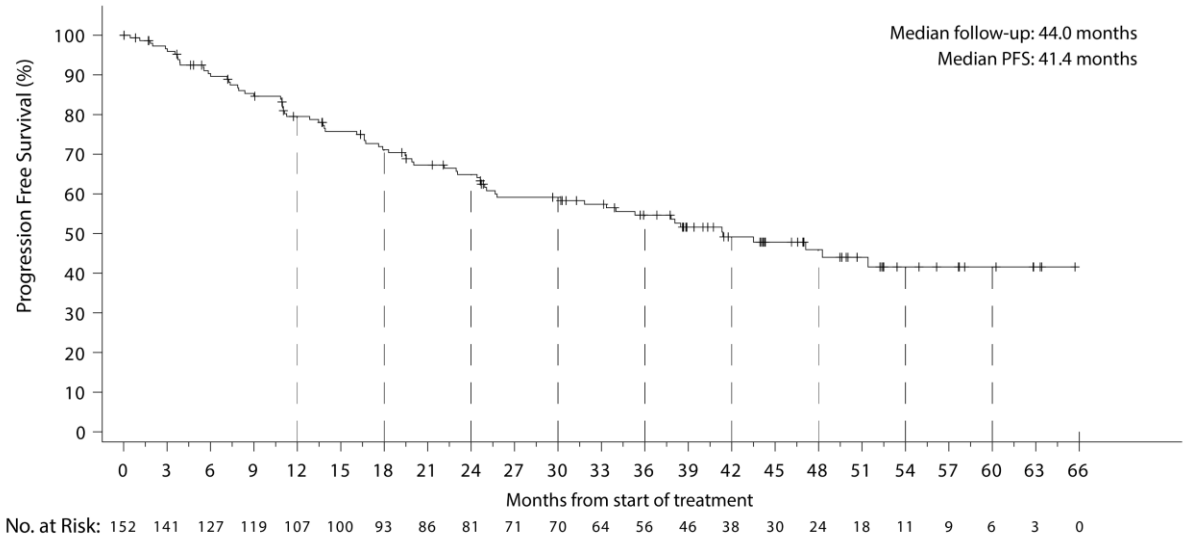
KM plots of PFS for the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are presented in Figure 13 and Figure 14, respectively.

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

	RET-mutant MTC prior cabozantinib/vandetanib N=152	*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	41.4	[redacted]
95% CI	30.2, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥12 months or more (95% CI)	79.5 (71.8, 85.3)	[redacted]
≥24 months or more (95% CI)	64.9 (56.2, 72.3)	[redacted]
≥36 months or more (95% CI)	54.6 (45.6, 62.8)	[redacted]
Duration of follow-up (months)		
Median	44.0	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Progression status (n, %)		
Disease progression	53 (34.9)	86 (29.2)
Died (no disease progression beforehand)	16 (10.5)	22 (7.5)
Censored	83 (54.6)	187 (63.4)

'*' 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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

Figure 13: KM plot of PFS based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population



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),[78] Wirth *et al* (2023).[73]

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

[redacted]

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).[78]

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 prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are summarised in Table 23. The rate of OS for the prior cabozantinib/vandetanib *RET*-mutant MTC population ranged from 87.8 (81.3, 92.1) at ≥12 months to 67.8 (59.4, 74.8) at ≥36 months. While median OS was reached in the prior cabozantinib/vandetanib *RET*-mutant MTC population (Table 23), this result was not considered meaningful due to the relatively short median follow-up duration of 46.9 months for OS.[74] OS results for the any-line MTC population were broadly consistent with the prior cabozantinib/vandetanib *RET*-mutant MTC population, with OS landmark rates for the any-line *RET*-mutant MTC population being slightly higher at later timepoints than the prior cabozantinib/vandetanib *RET*-mutant MTC population.

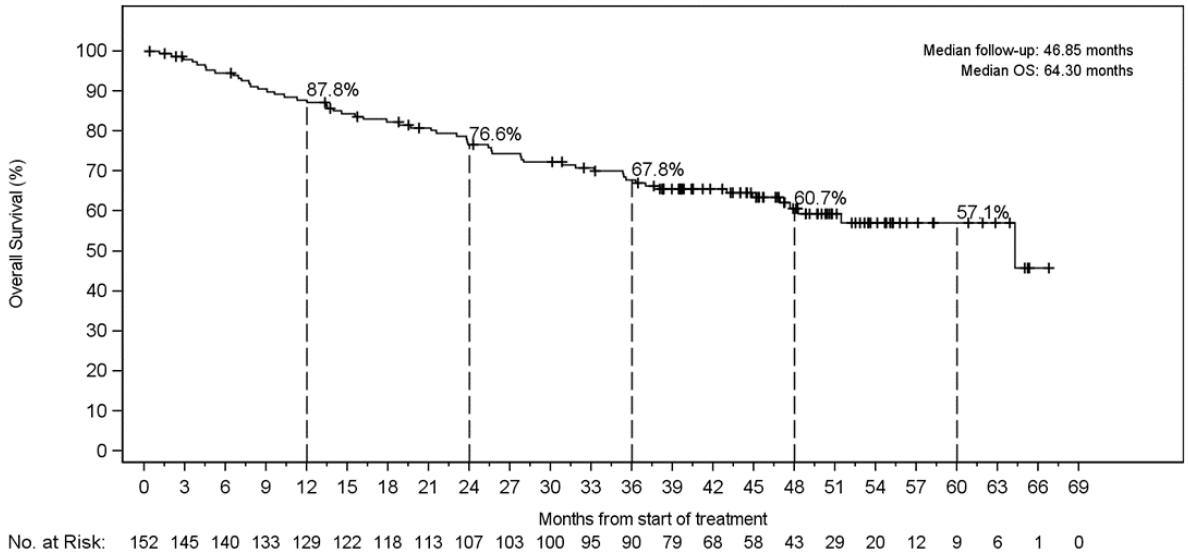
KM plots of OS for the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are shown in Figure 15 and Figure 16, respectively, with Figure 15 demonstrating that approximately half of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population were alive at the 13th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

Table 23: OS for the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population in the LIBRETTO-001 trial

	RET-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
Duration of overall survival (months)		
Median	64.3a	[redacted]
95% CI	48.3, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of overall survival		
≥12 months (95% CI)	87.8 (81.3, 92.1)	[redacted]
≥24 months (95% CI)	76.6 (68.8, 82.7)	[redacted]
≥36 months (95% CI)	67.8 (59.4, 74.8)	[redacted]
Duration of follow-up (months)		
Median	46.9	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Survival status (n, %)		
Dead	[redacted]	[redacted]
Censored	96 (63.2)	224 (75.9)

[a] Due to the median duration of follow-up for OS, median OS in the prior cabozantinib/vandetanib *RET*-mutant population is not considered meaningful and is expected to increase with increased follow up. '*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; MTC: medullary thyroid cancer; NE: not evaluable; NR: not reported; OS: overall survival; PD: progressive disease; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[78] Wirth *et al* (2024).[74]

Figure 15: KM plot of OS in the prior cabozantinib/vandetanib *RET*-mutant MTC population



Abbreviations: KM: Kaplan-Meier; MTC: medullary thyroid cancer; No.: number of patients; OS: overall survival; RET: rearranged during transfection.
Source: Wirth *et al* (2024).[74]

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).[78]

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.[86]

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.[86] 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.[87] 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] patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population. 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 patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population. The mean baseline score for physical, emotional, cognitive and social function subscales were each [redacted] points.[78] 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 of patients showing improvement/worsening, in the prior cabozantinib/vandetanib *RET*-mutant MTC population at Day 1 of Cycle 9

Subscale	Prior cabozantinib/vandetanib *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]

[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)[78]

Table 25: Proportion of patients with *RET*-mutant MTC who had received prior cabozantinib/vandetanib with improved or worsened EORTC-QLQ-C30 compared with baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		Prior cabozantinib/vandetanib *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. [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)[78]

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 M.2.

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 prior systemic therapy *RET*-fusion positive TC population and the any-line *RET* fusion-positive TC population are presented in Table 26. For the prior systemic therapy *RET* fusion-positive TC population, ORR was 85.4% (35/41, 95% CI: 70.8, 94.4), with 5 (12.2%) patients experiencing a CR and 30 (73.2%) patients experiencing a PR. CBR and DCR were both high in the prior systemic therapy *RET* fusion positive TC population, both with rates of 100.0% (41/41, 95% CI: 91.4, 100.0).[74] BOR and ORR results were similar in the any-line *RET* fusion-positive TC patient population compared to the prior systemic therapy *RET* fusion-positive TC population.[73]

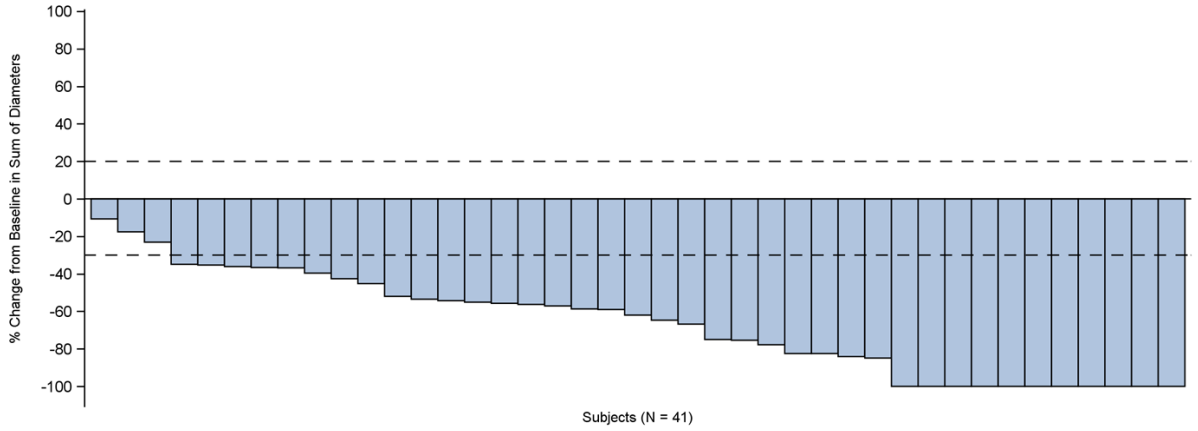
A waterfall plot illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment for the prior systemic therapy *RET*-fusion positive TC population is also shown in Figure 17, indicating that the sum of diameters of tumours were reduced >25% in all patients but three (N=38). A waterfall 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 prior systemic therapy N=41**	***RET* fusion-positive TC any-line population[a] N=65**
ORR[c]		
n (%)	35 (85.4)	58 (89.2)
95% CI	(70.8, 94.4)	[redacted]
BOR, n (%)		
CR	5 (12.2)	10 (15.4)
PR	30 (73.2)	48 (73.8)
SD	6 (14.6)	7 (10.8)
SD16+[d]	[redacted]	[redacted]
PD	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)
CBR (CR + PR + SD16+[b])[c]		
n (%)	41 (100.0)	65 (100.0)
95% CI	(91.4, 100.0)	[redacted]
DCR (CR + PR + SD)[d]		
N, (%)	41 (100.0)	65 (100.0)
95% CI	[redacted]	[redacted]

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations. [c] Response was confirmed by a repeat assessment every ≥28 days. [d] 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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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



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),[78] Wirth *et al* (2023).[73]

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).[78]

Duration of response

DOR results for the prior systemic therapy and the any-line *RET*-fusion positive TC populations are summarised in Table 27. After a median follow-up of 33.9 months, the median DOR by IRC was 26.7 months (95% CI: 12.1, NE). Durable response rates in the prior systemic therapy *RET* fusion-positive TC population were observed with 71.7% (95% CI: 52.4, 84.2) of patients in response for ≥12 months and 45.6% (95% CI: 25.6, 63.6) at ≥36 months.[74]

DOR results for the prior systemic therapy *RET* fusion-positive population were broadly consistent with the any-line TC population, with DOR landmark rates for the any-line *RET* fusion-positive TC population being slightly higher than the prior systemic therapy *RET* fusion-positive TC population. Additionally, median DOR was [redacted] (95% CI: [redacted]) in the any line population.

A KM plot of DOR for the prior systemic therapy *RET* fusion-positive TC population is presented in Figure 19, demonstrating similar response rates as the larger prior cabozantinib/vandetanib *RET*-mutant MTC population. For completeness, a KM plot of DOR for the any-line TC population is provided in Figure 20.

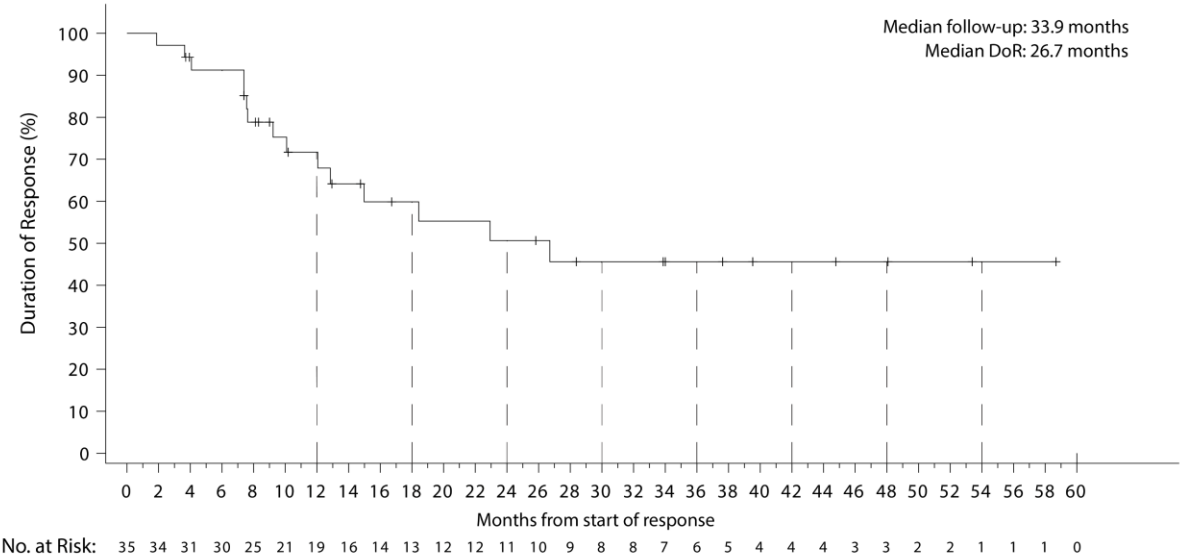
Table 27: DOR based on IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC prior systemic therapy N=41**	***RET* fusion-positive TC any-line population[a] N=65**
Responders (n)	35	58
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	26.7	[redacted]
95% CI	12.1, NE	[redacted]
Rate (%) of DOR		
≥12 months (95% CI)	71.7 (52.4, 84.2)	[redacted]
≥24 months (95% CI)	50.7 (30.4, 67.8)	[redacted]
≥36 months (95% CI)	45.6 (25.6, 63.6)	[redacted]
DOR follow-up (months)		
Median	33.9	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	12.9, 44.8	[redacted]

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations.
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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

Figure 19: KM plot of DOR based on IRC assessment for the prior systemic therapy *RET*-fusion positive TC population



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),[78] Wirth *et al* (2023).[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).[78]

Progression free survival

PFS results for the prior systemic therapy and the any-line *RET*-fusion positive TC populations are summarised in Table 28. After a median follow-up of 30.4 months, median PFS was 27.4 months (95% CI: 14.5, NE). In the prior systemic therapy *RET*-fusion positive TC population, [redacted] were alive without documented disease progression by IRC assessment at the DCO, with [redacted] progression events observed. Rates of PFS ranged from 70.6 (53.2, 82.6) for ≥12 months, to 49.5 (31.1, 65.4) at ≥36 months, reflecting the PFS rates observed in the larger *RET*-mutant MTC population.[73, 74]

PFS results were broadly consistent in the any-line TC patient population compared to the prior systemic therapy *RET* fusion-positive TC population. However, PFS landmark rates for the any-line *RET* fusion-positive population were slightly higher at later timepoints than the prior systemic therapy *RET* fusion-positive TC population. Additionally, median PFS was [redacted] (95% CI: [redacted] in the any-line population.

KM plots of PFS for the prior systemic therapy and the any-line *RET* fusion-positive TC populations are presented in Figure 21 and Figure 22, respectively.

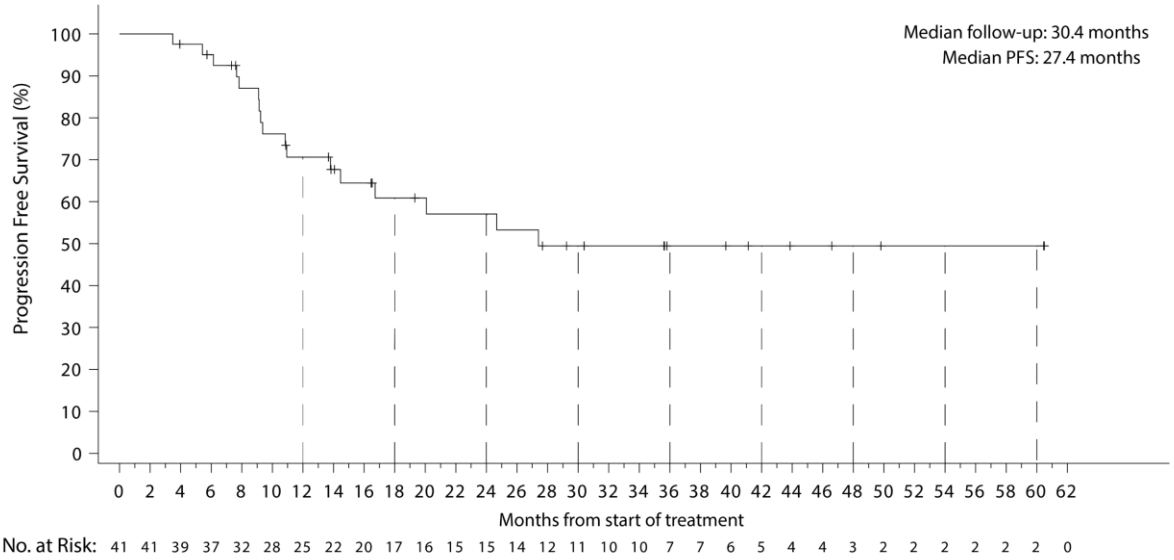
Table 28: PFS based on IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive TC prior systemic therapy N=41**	***RET* fusion-positive TC any-line population[a] N=65**
Reason censored (n, %)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without	[redacted]	[redacted]

documented PD		
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]	27.4	[redacted]
95% CI	14.5, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥12 months or more (95% CI)	70.6 (53.2, 82.6)	[redacted]
≥24 months or more (95% CI)	57.1 (38.6, 71.8)	[redacted]
≥36 months or more (95% CI)	49.5 (31.1, 65.4)	[redacted]
Duration of follow-up (months)		
Median	30.4	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Progression status (n, %)		
Disease progression	16 (39.0)	19 (29.2)
Died (no disease progression beforehand)	1 (2.4)	1 (1.5)
Censored	24 (58.5)	45 (69.2)

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations. '*' 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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

Figure 21: KM plot of PFS based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population



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),[78] Wirth *et al* (2023).[73]

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

[redacted]

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).[78]

Overall survival

OS results for the prior systemic therapy and the any-line *RET* fusion-positive TC populations are summarised in Table 29. After a median follow-up of 36.9 months, median OS was not reached (95% CI: 25.3, NE), with [redacted] patients alive at the 13th January 2023 DCO.[74] The rate of OS at ≥36 months was 65.5% (95% CI: 46.0, 79.4).

OS results were similar in the any-line *RET* fusion-positive TC patient population compared to the prior systemic therapy *RET* fusion-positive population, with median OS [redacted] and slightly higher landmark rates of OS at later timepoints.

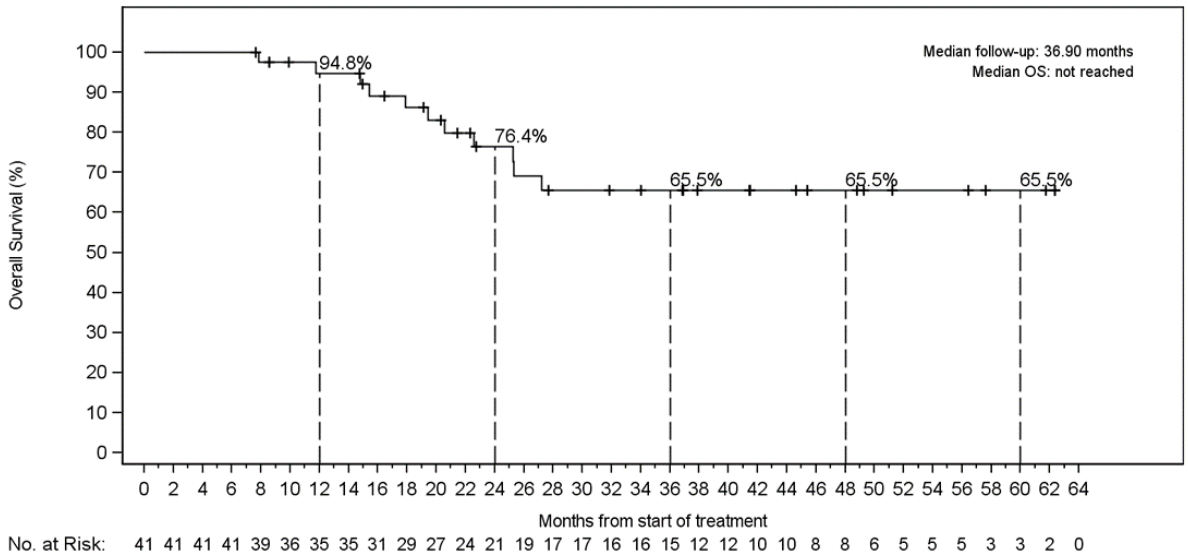
KM plots of OS for the prior systemic therapy and the any-line *RET*-fusion positive TC populations are shown in Figure 23 and Figure 24, demonstrating that the majority of patients were alive at the 13th January 2023 DCO in both populations.

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

	***RET* fusion-positive TC prior systemic therapy N=41**	***RET* fusion-positive TC any-line population[a] N=65**
Duration of OS (months)		
Median	NE	[redacted]
95% CI	25.3, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of OS		
≥12 months (95% CI)	94.8 (80.7, 98.7)	[redacted]
≥24 months (95% CI)	76.4 (58.1, 87.5)	[redacted]
≥36 months (95% CI)	65.5 (46.0, 79.4)	[redacted]
Duration of follow-up (months)		
Median	36.9	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Survival status (n, %)		
Dead	[redacted]	[redacted]
Censored	30 (73.2)	53 (81.5)

[a] The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations. '*' 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),[78] Wirth *et al* (2024).[74]

Figure 23: KM plot of OS for the prior systemic therapy *RET* fusion-positive TC population



Abbreviations: KM: Kaplan-Meier; No.: number of patients; OS: overall survival; RET: rearranged during transfection; TC: thyroid cancer.
Source: Wirth *et al* (2024).[74]

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

[redacted]

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] patients in the prior systemic therapy *RET* fusion-positive TC population.

The mean baseline score global health status/QoL subscale was [redacted] (SD=[redacted]) for eligible patients in the prior systemic therapy *RET* fusion-positive TC population. The mean baseline score for physical, emotional, cognitive, social and role function subscales were each [redacted] points.[78] 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, for patients in the prior systemic therapy *RET* fusion-positive TC population at Day 1 of Cycle 9

Subscale	Prior systemic therapy *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]

[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)[78]

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

QLQ-C30 Subscale, n (%)		Prior systemic therapy *RET* fusion-positive TC ([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. [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)[78]

B.2.6.3 Systemic Anti-Cancer Therapy Dataset

To support the recommendation of selpercatinib as a treatment for advanced *RET*-altered TC and MTC after prior systemic therapy into the CDF (TA742), real-world data collected via the SACT dataset are also available for selpercatinib as a treatment for *RET*-mutant MTC in UK clinical practice. However, no data are available for patients with *RET* fusion-positive TC in this data set.

Due to the immaturity of these data (median duration of OS follow-up: 12 months), the small sample size (N=18), and the lack of data for patients with *RET* fusion-positive TC, the SACT dataset were not deemed suitable to inform efficacy estimates in this submission. The LIBRETTO-001 trial can therefore be considered the more robust source of evidence for selpercatinib in the populations of interest in this submission. The SACT data are provided in the reference pack alongside this submission for completeness.[75]

B.2.7 *Subgroup analysis*

ORR and DOR, based on IRC assessment, were analysed by several demographic variables, type of *RET* mutation, type of molecular assay used, and number and type of prior therapies in the both the prior cabozantinib/vandetanib *RET*-mutant MTC population and the prior systemic therapy *RET* fusion-positive TC population, 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 prior cabozantinib/vandetanib *RET*-mutant MTC population is presented in Table 32. In some subgroups, DOR was [redacted]. In the remaining subgroups, median DOR was broadly consistent with the overall population.

Table 32: ORR and DOR by demographics based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (95% CI)
Overall	152	118	77.6 (70.2, 84.0)	[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; SD: stable disease.
Sources: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[78] Wirth *et al* (2024).[74]

Subgroup analysis by *RET* mutation

Results of the subgroup analysis of ORR and DOR by type of *RET* mutation are presented in Table 33. ORR was broadly consistent for patients with different *RET* mutations. However, in patients with a V804M or V804L mutation, ORR was slightly higher. Median DOR was [redacted] in some subgroups, whilst in the remaining subgroups, median DOR was broadly consistent with the overall population.

The ORR and DOR by type of molecular test are also presented in Table 33. With the exception of patients with the NGS on tumour, ORR was slightly lower than the overall population. Median DOR was [redacted] in some subgroups, whilst in the remaining subgroups, median DOR was broadly consistent with the overall population.

Table 33: ORR and DOR based on IRC assessment by *RET* mutation type and type of molecular assay for the prior cabozantinib/vandetanib *RET*-mutant MTC population

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	152	118	77.6 (70.2, 84.0)	[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),[78] Wirth *et al* (2024).[74]

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 34. ORR was broadly consistent across all subgroups. Median DOR was [redacted] in some subgroups, but in the remaining subgroups, median DOR was similar to the overall population.

Table 34: ORR and DOR by number and type of prior therapy based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	152	118	77.6 (70.2, 84.0)	[redacted]
Number of prior therapies				
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),[78] Wirth *et al* (2024).[74]

Forest plot summary for ORR analyses

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

Figure 25: Forest plot of ORR in subgroup populations based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population

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).[78]

B.2.7.2 *RET* fusion-positive thyroid cancer

Subgroup analysis by demographic variables

ORR and DOR by demographics for the prior systemic therapy *RET*-fusion positive TC population is presented in Table 35. For some subgroups, DOR was [redacted]. However, ORR was broadly consistent across the remaining subgroups, with any variation likely due to low patient numbers in several of the demographic subgroups.

Table 35: ORR and DOR by demographics based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population

Baseline characteristic	N	Responders (n)	ORR, % (95% CI)	DOR, months (95% CI)
Overall	41	35	85.4 (70.8, 94.4)	[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),[78] Wirth *et al* (2024).[74]

Subgroup analysis by *RET* mutation

ORR and DOR by type of *RET* mutation for the prior systemic therapy *RET* fusion-positive TC population are presented in Table 36. DOR by mutation type was [redacted] for several fusion types. The ORR and DOR by type of molecular test are also presented in Table 36.

Table 36: ORR and DOR by *RET* mutation type and type of molecular assay based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population

Baseline characteristic	N	Responders	ORR[a], % (95% CI)	DOR, months (range)
Overall	41	35	85.4 (70.8, 94.4)	[redacted]
***RET* mutation type**				
CCDC6	[redacted]	[redacted]	[redacted]	[redacted]
NCOA4	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
C10ORF118	[redacted]	[redacted]	[redacted]	[redacted]
ERC1	[redacted]	[redacted]	[redacted]	[redacted]
GOLGA5	[redacted]	[redacted]	[redacted]	[redacted]
KTN1	[redacted]	[redacted]	[redacted]	[redacted]
RUFY3	[redacted]	[redacted]	[redacted]	[redacted]

SPECC1L	[redacted]	[redacted]	[redacted]	[redacted]
TRIM24	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[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]

[a] Percentage ORR is not calculated when number of patients is ≤2, best overall response is shown instead.
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),[78] Wirth *et al* (2024).[74]

Subgroup analysis by number and type of prior therapy

ORR and DOR by number or type of prior therapy are presented in Table 37. ORR was broadly consistent across the number of prior therapies. DOR was [redacted] for the two prior therapies subgroup ([redacted]). There was some variation across the other prior therapies subgroups, which may be due to the small patient numbers associated with these subgroups.

Table 37: ORR and DOR by number and type of prior therapy based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	41	35	85.4 (70.8, 94.4)	[redacted]
Number of prior therapies				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]

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),[78] Wirth *et al* (2024).[74]

Forest plot summary for ORR analyses

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

Figure 26: Forest plot of ORR in subgroup populations based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population

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).[78]

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 BSC, the relevant comparator for *RET*-mutant MTC and *RET* fusion-positive TC in UK clinical practice.
- ITCs for selpercatinib versus BSC in *RET*-mutant MTC were based on LIBRETTO-001 versus the EXAM trial. ITCs for selpercatinib versus BSC in *RET* fusion-positive TC were based on LIBRETTO-001 versus the SELECT trial.

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 DSU TSD 18.[76, 88, 89]
- 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 placebo (n=45) in the EXAM trial were compared to the weighted curve for the any-line LIBRETTO-001 population.[54]
- 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: 0.11 [95% CI: 0.07, 0.18; p<0.001]; PFS HR: 0.05 [95% CI: 0.03, 0.09; p<0.001]).

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 trial (SELECT). As such, naïve ITCs were conducted to generate comparative efficacy estimates for selpercatinib versus BSC.
    - Following a feasibility assessment, the placebo arm of the SELECT trial 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.[3, 27]
- 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).
    - In order to facilitate comparisons with the SELECT trial, the pooled, any-line TC population (n=65) from the LIBRETTO-001 trial was used in the ITCs, to more closely match the SELECT ITT population.
- 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 with narrow confidence intervals (OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; PFS 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.[76]
- Selpercatinib demonstrates clinically meaningful and statistically significant treatment benefits versus BSC, the relevant comparator in UK clinical practice for *RET*-mutant MTC and *RET* fusion-positive TC.

As discussed in Section B.2.1, 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.

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 and the *RET* fusion-positive TC population, the only relevant comparator in UK clinical practice is 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 require systemic therapy after prior cabozantinib/vandetanib, the relevant comparator in UK clinical practice is BSC. As discussed in Section B.2.1, an SLR and a subsequent update have been conducted to identify all relevant clinical evidence on the efficacy and safety of selpercatinib and 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 two trials were identified that were RCTs (including a placebo arm, to be used as a proxy for BSC) and reported results in *RET*-mutant populations: the EXAM trial and the ZETA trial (Appendix D.1.4).[54, 90, 91] However, the ZETA trial did not report PFS and OS KM results for a *RET*-mutant subgroup, only results for ORR. As several covariates relevant to the MAIC analysis (Section B.2.9.1) were not reported in the ZETA trial, and treatment crossover from the placebo arm to the vandetanib arm was permitted in the trial, potentially confounding OS results, the EXAM trial was selected as the most appropriate data source to compare selpercatinib versus BSC, using the placebo arm as a proxy.[54, 90, 91]

The EXAM trial was an international, double-blind, randomised placebo-controlled Phase III RCT 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.[91] 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 population (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 to inform the efficacy of selpercatinib.

Baseline characteristics were only available for a *RET*-mutant subgroup in the cabozantinib treatment arm of the EXAM trial.[54] In the absence of baseline data for a *RET*-mutant subgroup in the placebo arm of the EXAM trial, the characteristics of the LIBRETTO-001 any-line MTC population and the *RET*-mutant population of the cabozantinib arm of EXAM 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 are presented in Appendix D.1.4. 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 38. The any-line MTC population from the LIBRETTO-001 trial was compared to the *RET*-mutant subgroup of the cabozantinib arm in the EXAM trial, in the absence of published baseline characteristics for a *RET*-mutant subgroup of the placebo arm. It is assumed that baseline characteristics of the *RET*-mutant placebo treatment arm would be comparable to those in the *RET*-mutant cabozantinib treatment arm of EXAM.

Key differences in the patient population characteristics, prior to matching, include the following:

- The LIBRETTO-001 any-line trial population (mean age: 56.0 years) is slightly older than the cabozantinib arm of the EXAM trial (mean age: 55.0 years)
- The percentage of male patients in the LIBRETTO-001 any-line population (61.0%) is slightly lower than the cabozantinib arm of the EXAM trial (68.2%)
- A lower proportion of patients had an ECOG performance status of 0 in the LIBRETTO-001 any-line population (37.6%) compared with the cabozantinib arm of the EXAM trial (61.7%)
- The proportion of patients in the LIBRETTO-001 any-line population with prior MKI/TKI therapy (54.6%) was substantially higher than the cabozantinib arm of the EXAM trial (21.5%)
- The proportion of patients in the LIBRETTO-001 trial who had never smoked (59.7%) was higher than the cabozantinib arm of the EXAM trial (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 the first-line submission for selpercatinib, NICE ID6183.[69] The findings identified by the SLR for prognostic factors and treatment effect modifiers are summarised in Appendix D.1.4, 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 a higher proportion of patients with prior therapy. The proportion of patients who were female and who had never smoked was higher in LIBRETTO-001.

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 placebo. The placebo arm of the EXAM trial is considered a suitable proxy for BSC, as determined in TA516 and TA742.[3, 26]

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, 92]

Due to similarities of baseline characteristics of the EXAM cabozantinib trial population and the any-line MTC population from LIBRETTO-001, all patients in the any-line MTC population from LIBRETTO-001 were then included in the matched set.[69] This approach was supported clinical experts in thyroid cancer interviewed to support the first-line appraisal for selpercatinib, NICE ID6183, who noted the similarity between the two populations after matching.[69]

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.[76, 88, 89]

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.1.4).[69] The variables included in the adjustment were:

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

Clinical experts in thyroid cancer interviewed to support the development of NICE ID6183, which also conducted ITCs using the any-line MTC population in LIBRETT0-001, confirmed that this list of variables covered all clinically important prognostic variables and treatment effect modifiers.[69]

To balance the baseline characteristics between LIBRETTO-001 and EXAM, the selected LIBRETTO-001 patients were assigned weights such that their weighted mean baseline characteristics exactly matched those reported for patients in EXAM. Specifically, matching was performed for the any-line MTC population from the LIBRETTO-001 trial and the *RET*-mutant subgroup treated with cabozantinib in the EXAM trial, due to the availability of baseline characteristics for the *RET*-mutant subgroup treated with cabozantinib. Published baseline characteristics for a *RET*-mutant subgroup treated with placebo in the EXAM trial are not available, however it is assumed that baseline characteristics of a *RET*-mutant placebo treatment arm would be comparable to those in the *RET*-mutant cabozantinib treatment arm of EXAM.[54]

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 curve for the *RET*-mutant population receiving placebo (n=62) in the EXAM trial digitised from Sherman *et al.* (2016) was compared to the weighted curve for the any-line LIBRETTO-001 population[92]

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 curve for *RET* M918T-positive patients receiving placebo (n=45) in the EXAM trial digitised from Schlumberger *et al.* (2017) was compared to the weighted curve for the any-line LIBRETTO-001 population as a proxy for the *RET*-mutant subgroup[54]

Results of the MAIC

Baseline characteristics

A summary of the baseline characteristics of the LIBRETTO-001 any-line MTC population (prior to and after matching), the *RET*-mutant population in the EXAM trial receiving cabozantinib and the placebo arm of the EXAM trial included in the MAIC are provided in Table 38. Matching was performed between the any-line MTC population in the LIBRETTO-001 trial and the *RET*-mutant subgroup treated with cabozantinib in the EXAM trial, in the absence of baseline characteristics

available for a *RET*-mutant subgroup treated with placebo in the EXAM trial. 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 LIBRETTO-001 any-line population and the *RET*-mutant subgroup in the EXAM trial treated with cabozantinib.

Table 38 presents baseline characteristics of the LIBRETTO-001 any-line *RET*-mutant MTC population before and after adjustment, the *RET*-mutant population treated with cabozantinib in the EXAM trial and the placebo arm of the EXAM trial. After matching, sex and ECOG performance score were broadly aligned between the LIBRETTO-001 any-line MTC population and the placebo arm of the EXAM trial. Importantly, adjustment resulted in the proportion of patients with prior TKI/MKI treatment between the LIBRETTO-001 any-line MTC population and the placebo arm of the EXAM trial being closely aligned. However, after matching, *RET* M918T positive status remained unbalanced; the LIBRETTO-001 any-line MTC population had a higher proportion of patients with *RET* M918T mutation-positive disease versus the placebo arm of the EXAM trial. After weighting, the effective sample size (N_{eff}) for the MTC any-line population in LIBRETTO-001 was 157.

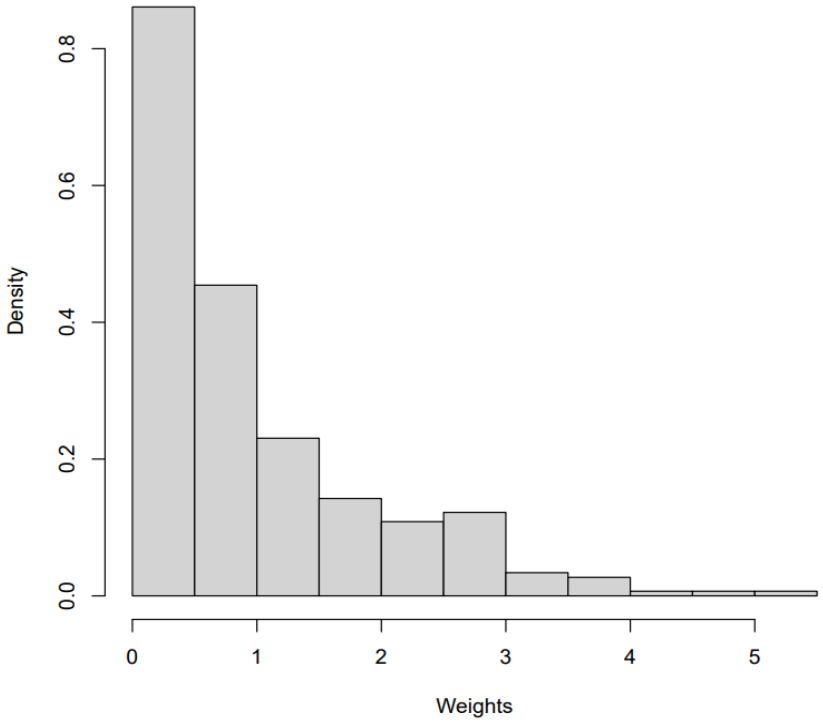
The distribution of weights is presented in Figure 27, indicating no evidence of extreme weights. Weights were rescaled so that they were relative to the original units weights of each individual, in line with the methodology proposed in NICE TSD18.[76] Rescaling had very limited impact on the results.

Table 38: 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}=157)	EXAM *RET*-mutant cabozantinib (N=107)	EXAM Placebo (N=111)
Age, mean (SD)	56.0 ± 15.1	55.0 (15.2)	55.0 (15.2)	NR*
Weight (kg), mean (SD)	73.1 ± 21.0	74.0 (21.0)	74.0 (21.0)	NR
ECOG PS 0 (%)	37.6	61.7	61.7	50.5
Sex (% male)	61.0	68.2	68.2	63.1
Smoking (% never)	59.7	51.4	51.4	NR
RET M918T mutation positive (%)	62.7	74.6	74.6	52.3
Prior TKI/MKI therapy (%)	54.6	21.5	21.5	21.6

[a] Mean age for patients in the placebo arm of the EXAM trial is not available; Median age is 55.0 years.
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: Jen et al (2023),[93] Raez et al (2023).[80] Elisei, et al (2013).[91]

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 placebo in EXAM are presented in Table 39 (using a Cox regression model), with results for selpercatinib versus cabozantinib also presented for completeness. 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 N.

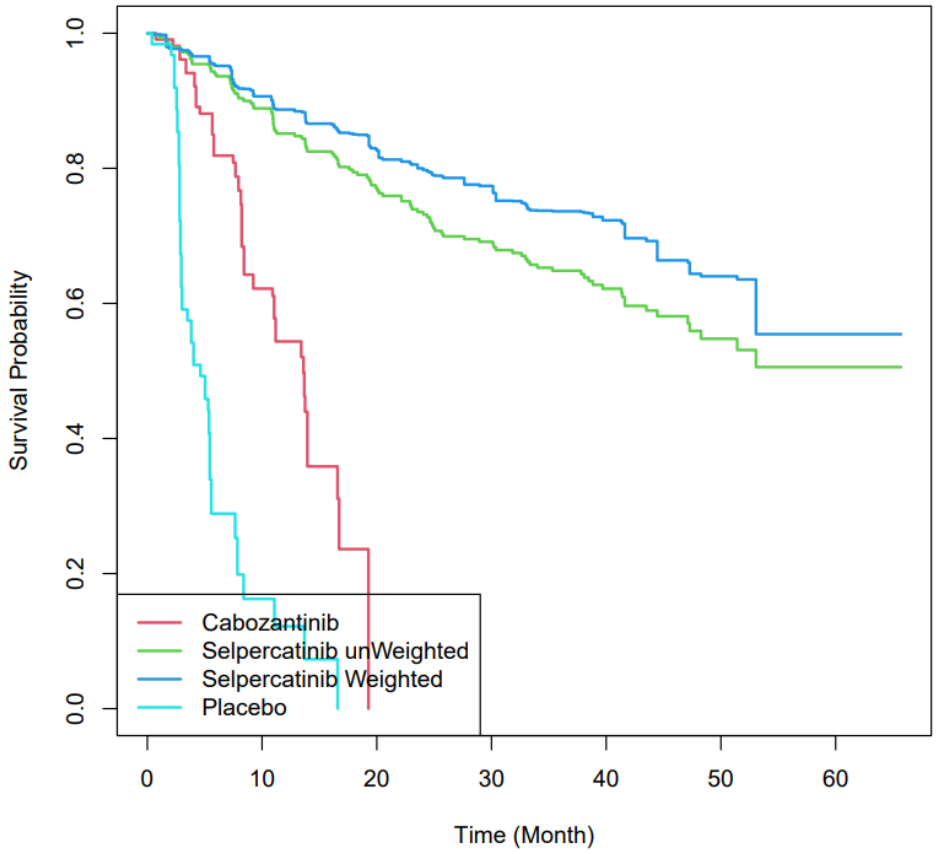
After weighting, the differences between treatment benefit in PFS remained significant and clinically meaningful for selpercatinib versus BSC (placebo) (HR: 0.05; 95% CI: 0.03, 0.09; p<0.001). The differences between treatments in OS after weighting were also significant for selpercatinib versus BSC (placebo) (HR: 0.11; 95% CI: 0.07, 0.18; p<0.001).

Table 39: Comparison of PFS and OS for selpercatinib (LIBRETTO-001) versus placebo and cabozantinib (EXAM) before and after matching

	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Selpercatinib versus cabozantinib				
Unweighted	0.12 (0.09, 0.17)	<0.001	0.38 (0.26, 0.56)	<0.001
Weighted	0.08 (0.05, 0.13)	<0.001	0.20 (0.13, 0.32)	<0.001
Selpercatinib versus BSC (placebo)				
Unweighted	0.07 (0.04, 0.10)	<0.001	0.21 (0.14, 0.32)	<0.001
Weighted	0.05 (0.03, 0.09)	<0.001	0.11 (0.07, 0.18)	<0.001

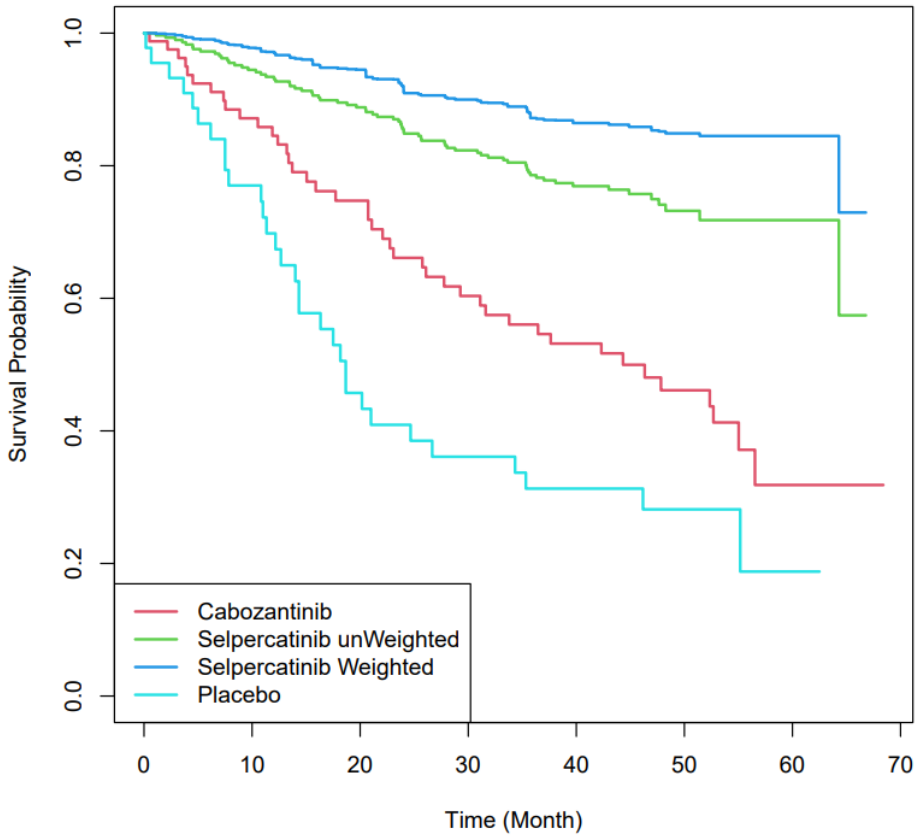
Abbreviations: BSC: best supportive care; CI: confidence intervals; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.
Source: Jen et al. (2023)[93] Elisei et al, (2013)[53]

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.
Source: Jen et al (2023)[93]

Figure 29: OS for selpercatinib (LIBRETTO-001) versus cabozantinib and placebo (EXAM *RET* M918T-positive subgroup) before and after weighting



Test for PH assumption in OS was not rejected before and after weighting (p>0.05) for selpercatinib versus placebo (Appendix N).
Abbreviations: KM: Kaplan-Meier; OS: overall survival; PFS: progression free survival; PH: proportional hazards.
Source: Jen et al (2023)[93]

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, BSC represents the relevant comparator for selpercatinib. Following the initial feasibility assessment, the SELECT (lenvatinib versus placebo) and DECISION (sorafenib versus placebo) trials were identified as potential data sources for BSC in patients with advanced TC.

Both the SELECT and the DECISION trials were Phase III, double-blind, parallel-group RCTs enrolling patients with DTC. In both trials, treatment crossover from the placebo to the active treatment arm were permitted at disease progression.[55, 94] Adjusted KM OS curves, using RPSFT, were available for the SELECT trial to account for this treatment crossover. However, adjusted data were not available for the DECISION trial. As such, due to the potential confounding to OS results introduced by crossover in the DECISION trial, the SELECT trial was selected to represent the most appropriate proxy for BSC, which is aligned with the approach accepted in TA535 and TA742.[3, 27]

Feasibility assessment

Trial and patient characteristics

The SELECT trial included 261 adult patients with DTC (including a PTC sub-population) with evidence of radioactive iodine-refractory disease.[55] Patients received lenvatinib 24 mg orally QD, or a matching placebo. A top-line summary of the SELECT trial design is presented in Appendix D.1.4.

Baseline characteristics of patients in the LIBRETTO-001 and SELECT trials are presented in Table 40. Subgroup analyses for a *RET* fusion-positive population were not reported for OS or PFS in the SELECT trial. As such, baseline characteristics are reported for the ITT populations. In the SELECT trial, patients were required to be refractory to radioactive iodine locally advanced or metastatic DTC for inclusion and the trial only allowed patients with one or no prior TKI/MKI therapy to be included. The characteristics of the ITT population are presented for patients with advanced DTC receiving placebo.

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. Due to the lack of OS data available in a prior systemic treatment subgroup in the SELECT trial, the any-line pooled TC population from LIBRETTO-001 (n=65 patients) was selected for comparison against the ITT population in the SELECT trial in the ITC.

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

- [redacted]% of patients have advanced or metastatic *RET*-fusion positive TC in LIBRETTO-001, while no data are reported for a *RET*-fusion positive subgroup in the SELECT trial
- A higher proportion of patients were diagnosed with PTC in the LIBRETTO-001 trial (83.1%), compared with both the placebo arm (51.9%) of the SELECT trial
- In LIBRETTO-001 (any-line), a higher proportion of patients had received at least 1 prior TKI or MKI (53.8%) compared with the placebo arm (20.6%) of the SELECT trial
- 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 placebo arm (51.9%) of the SELECT trial

During validation interviews conducted with clinical experts, the experts stated that the presented baseline characteristics of the any-line LIBRETTO-001 TC population and the SELECT trial were broadly similar and no clinically important differences were identified with the exception of prior therapies received by patients.

However, one clinical expert highlighted that the ECOG performance status of patients in the LIBRETT0-001 trial was generally poorer compared with the SELECT trial. This would be expected to bias the ITC results against selpercatinib, when comparing with the SELECT trial. The clinical experts also noted that the increased proportion of patients with PTC in the LIBRETTO-001 trial versus the SELECT trial 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.[35, 69]

Table 40: Baseline characteristics of patients with TC enrolled in the LIBRETTO-001 and SELECT, trials

Characteristic	LIBRETTO-001 (*RET*-fusion positive TC) Selpercatinib (any-line) N=65	SELECT Placebo (ITT population) N=131
Median age, years (range)	59 (20, 88)	61 (21, 81)
Number (%) male	32 (49.2)	75 (57.3)
Ethnicity		
White	42 (64.6)	103 (78.6)
Black of African American	3 (4.6)	4 (3.1)
Asian	13 (20)	24 (18.1)
Other	[redacted]	0
Missing or uncodeable	[redacted]	NR
Region, n (%)		
Europe	[redacted]	64 (48.9)
North America	[redacted]	39 (29.8)
Other	[redacted]	28 (21.4)
Median time from initial diagnosis, months (range)	[redacted]	73.9 (6.0, 484.8)
ECOG performance status, n (%)		
0	25 (38.5)	68 (51.9)
1	36 (55.4)	61 (46.6)
2	4 (6.2)	2 (1.5)
3	0 (0.0)	0 (0.0)
Not available	0 (0.0)	0 (0.0)
Histology, n (%)		
Papillary	54 (83.1)	68 (51.9)
Poorly differentiated	6 (9.2)	19 (14.5)
Follicular, not Hürthle cell	0 (0.0)	22 (16.8)
Hürthle cell	1 (1.5)	22 (16.8)
Other	4 (6.2)*	0 (0.0)
Missing or non-diagnosed	0 (0.0)	0 (0.0)
Metastases, n (%)		
Locoregional	[redacted]	0 (0.0)
Distant	[redacted]	131 (100)
Prior MKI/TKI therapy		
Any prior therapy	35 (53.8)	27 (20.6)
Cabozantinib	1 (1.5)	NR
Vandetanib	1 (1.5)	NR
Sorafenib	9 (13.8)	NR

Lenvatinib	26 (40)	NR
Other MKI	7 (10.8)	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),[80] Wirth *et al* (2024).[74]

Crossover between treatment arms

Patients in the placebo arm were allowed to crossover to lenvatinib post-progression and continue in an open-label nature in the SELECT trial. Among the 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. KM OS curves were however adjusted to account for this treatment crossover (using RPSFT).

Summary of feasibility assessment

As discussed above, data from the LIBRETTO-001 trial are available for patients with *RET* fusion-positive advanced TC who had received prior systemic therapy (n=41). Although data on ORR and PFS are available for a prior systemic therapy population in SELECT, OS KM data for a prior systemic therapy population are not available. Therefore, an ITC was conducted to calculate comparative PFS and OS for selpercatinib versus BSC (using the placebo arm of SELECT as a proxy), using the pooled any-line TC population in LIBRETTO-001 (n=65) and the placebo arm of the ITT population in SELECT (n=131).[3]

The SELECT trial did not report outcomes in a *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.[41, 42] However, 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.[69]

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 placebo (from the SELECT trial) 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 aggregate data from the ITT population treated with placebo in the SELECT trial.

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 comparator (placebo). Non-parametric log-rank tests were used to evaluate statistical significance.

Progression free survival

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 population treated with placebo in the SELECT trial are considered in this section.

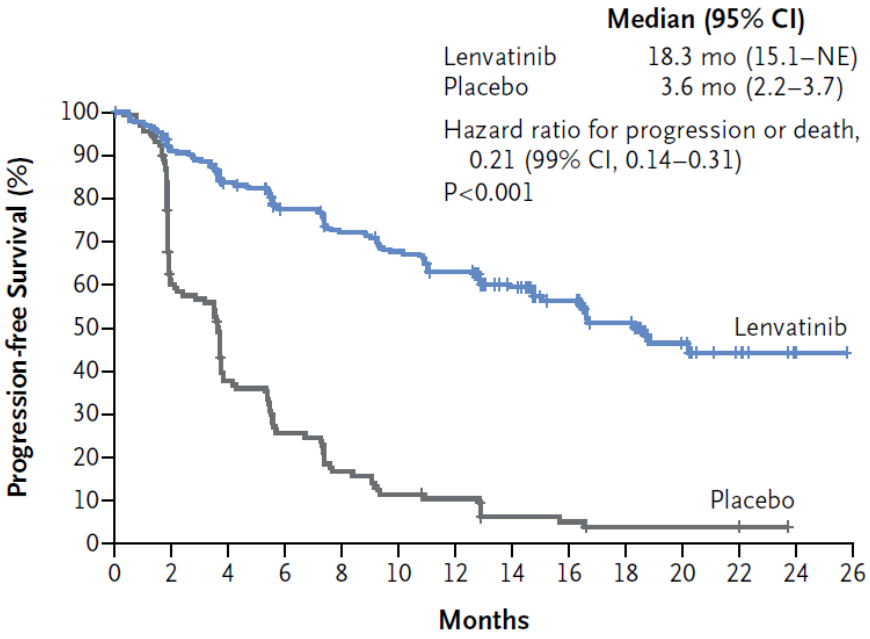
An overview of the PFS data for the LIBRETTO-001 and SELECT trials is presented in Table 41. A KM curve of PFS placebo (from SELECT) is presented in Figure 30 and the KM curve of PFS for the any-line TC population from selpercatinib is presented in Figure 20, Section B.2.6.2.

Table 41: PFS for the LIBRETTO-001 and SELECT trials

	LIBRETTO-001 (*RET*-fusion positive TC) Selpercatinib (any-line) (N=65)	**SELECT Placebo (ITT population) (N=131)**
Median PFS (95% CI), months	[redacted]	3.6 (2.2, 3.7)
PFS rate (%)		
6 months (95% CI)	[redacted]	25.4 (18.0, 33.6)
12 months (95% CI)	[redacted]	10.5 (5.7, 16.9)
18 months (95% CI)	[redacted]	3.8 (1.1, 9.2)
24 months (95% CI)	[redacted]	NE
Median follow-up duration (months)	[redacted]	17.4[a]

[a] Schlumberger *et al.* (2015) reports median follow-up for lenvatinib and placebo but it does not specify for which outcome.
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),[80], Schlumberger *et al* (2015).[55]

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



No. at Risk

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

Abbreviations: CI: confidence interval; NE: not estimated; PFS: progression-free survival.
Source: Schlumberger *et al.* (2015)[55]

Overall survival

For the SELECT trial, OS was only reported for the overall ITT population. A summary of OS results from the LIBRETTO-001 and SELECT trials are provided in Table 42.

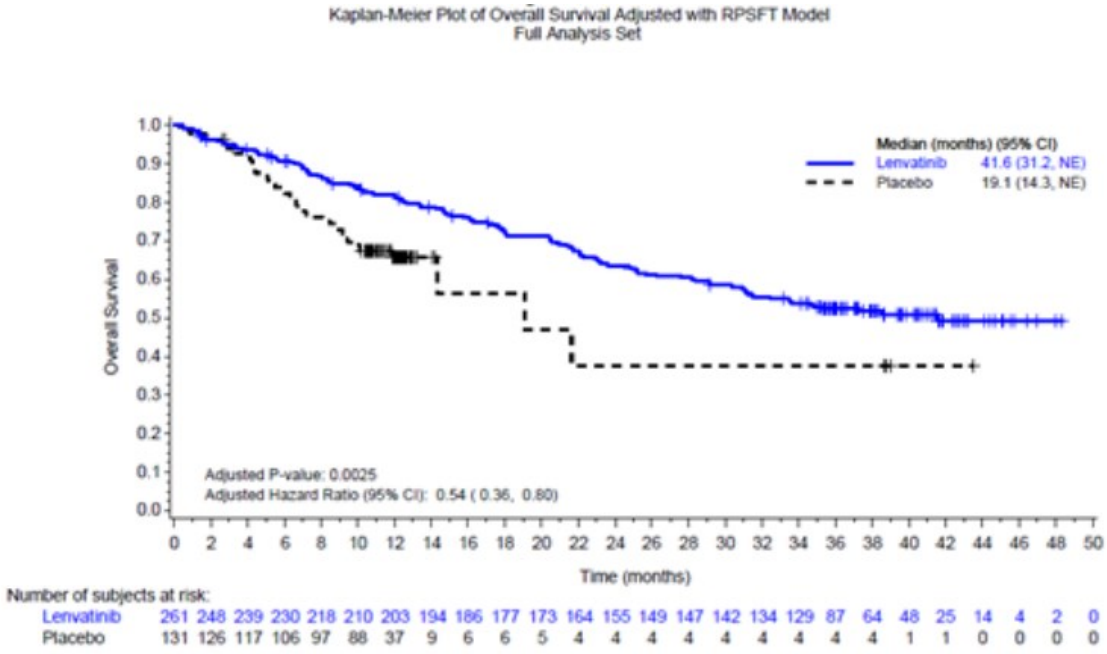
Patients in the placebo arm were allowed to cross over to lenvatinib at disease progression in SELECT. The majority of patients in the placebo arm crossed over (109 [95.6%] of patents who had experienced tumour progression).[54] This likely affected the OS of the control arm and was addressed by adjusting outcomes using a RPSFT model for patients receiving placebo.[95] KM curves for OS from SELECT before and after adjustment are presented in Figure 31.[27]

Table 42: OS in the LIBRETTO-001 and SELECT trials

	LIBRETTO-001 (*RET*-fusion positive TC) Selpercatinib (any-line) N=65	SELECT Placebo (ITT) N=131
Median OS (95% CI), months	[redacted]	*34.5 (21.7, NE)
OS rate (%)		
6 months (95% CI)	[redacted]	NR
12 months (95% CI)	[redacted]	NR
18 months (95% CI)	[redacted]	NR
24 months (95% CI)	[redacted]	NR
Median follow-up duration (months)	[redacted]	Data cut-off date: 21 August 2015[a]

*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.
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR#: not reported; NR: not reached; NE: not estimable; OS: overall survival; RPSFT: Rank-preserving structural failure time.
Sources: Raez *et al* (2023),[80] Schlumberger *et al*. (2015)[55]

Figure 31: 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.[95]

Results of the ITC

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

The comparison demonstrates a statistically significant improvement in both PFS and OS for selpercatinib versus BSC (placebo) with narrow confidence intervals (PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]; OS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]).

Table 43: Comparison of PFS and OS for selpercatinib (LIBRETTO-001, any-line) versus placebo (SELECT, ITT population)

Treatment comparison	HR (95% CI)	p-value
PFS: selpercatinib versus BSC (placebo)	[redacted]	[redacted]
OS: selpercatinib versus BSC (placebo)	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free 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,[76] 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 BSC, in line with the approaches used and accepted as part of NICE TA742.[3, 76]

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 NICE ID6183, which also conducted a MAIC using the LIBRETTO-001 any-line MTC population and the EXAM trial, 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.[69] It is assumed that baseline characteristics for the *RET*-mutant cabozantinib arm of the EXAM trial are similar to the *RET*-mutant placebo arm of the EXAM trial, as this was a randomised trial. Therefore, matching of the any-line MTC population in LIBRETTO-001 to the *RET*-mutant subgroup of the cabozantinib arm in the EXAM trial is expected to align baseline characteristics versus the *RET*-mutant placebo arm of the EXAM trial, though baseline characteristics for this subgroup were not available.

The MAICs were limited by comparator data availability. Firstly, clinical effectiveness results are not reported specifically for patients who had received prior systemic therapy in the *RET*-mutant subgroup of the EXAM trial. As such, it was not possible to conduct a MAIC using data specific to a population with *RET*-mutant MTC who had received prior systemic therapy. 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 any-line MTC LIBRETTO-001

population and the *RET*-mutant cabozantinib arm of the EXAM trial 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]

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). This approach was chosen in the absence of baseline characteristics reported for a *RET*-mutant subgroup in the placebo arm of the EXAM trial. The assumption was made that the baseline characteristics of the M918T-positive and *RET* mutation-positive cabozantinib groups were equivalent; in addition, it was assumed that baseline characteristics of the *RET*-mutant cabozantinib treatment arm were equivalent to those for the *RET*-mutant placebo treatment arm in the EXAM trial.

RET fusion-positive TC

As outlined above, naïve comparisons were conducted to derive comparative efficacy estimates for selpercatinib versus placebo in the *RET* fusion-positive TC subgroup, due to the small patient numbers in all trials and lack of comparability between LIBRETTO-001 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 the ongoing first-line submission for selpercatinib (ID6132), UK clinical experts confirmed that the baseline characteristics of the selpercatinib and SELECT trial can be considered broadly comparable.[69]

As with the MAIC conducted for the *RET*-mutant MTC population, the comparative efficacy estimates for selpercatinib versus BSC were limited by comparator data availability. Firstly, the SELECT trial was not limited to a *RET* fusion-positive population, and as outlined in Section B.1.3, 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 may not be generalisable to *RET* fusion-positive TC. Additionally, data for a prior systemic therapy population in the SELECT trial were not available for all endpoints of interest, and therefore the placebo arm of the ITT population of the SELECT trial was used in the ITC.

Accordingly, the proportion of patients who had not received prior systemic therapy differed between trials, which was not adjusted for in the naïve comparisons. Given the higher proportion of patients receiving prior systemic therapy in the any-line *RET* fusion-positive TC patient population in the LIBRETTO-001 trial versus the placebo arm of the ITT population in the SELECT trial, this difference may bias results against selpercatinib, as the LIBRETTO-001 patient population includes more 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 than patients in the SELECT trial; this conclusion is supported by clinical expert opinion obtained to support the ongoing appraisal for selpercatinib in untreated thyroid cancer, ID6132, who indicated that the lower proportion of patients in the LIBRETTO-001 trial with an ECOG performance score >0 may bias results against selpercatinib when compared with the SELECT trial.

Although the SELECT trial was selected as the source of BSC efficacy data in favour of the DECISION trial due to the availability of RPSFT-adjusted OS curves, OS may have been confounded by crossover due to the permission of crossover from the lenvatinib arm to the placebo arm in SELECT.

Summary of the results of the ITCs

For the comparison of selpercatinib versus BSC (using placebo as a proxy) in the *RET*-mutant MTC population, the results of the MAIC demonstrate a statistically significant and clinically meaningful treatment benefit in terms of both OS and PFS (OS HR: 0.11 [95% CI: 0.07, 0.18; p<0.001]; PFS HR: 0.05 [95% CI: 0.03, 0.09; p<0.001]), demonstrating a reduction in the risk of death and progression for patients receiving selpercatinib versus BSC of 89% and 95%, respectively. 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 and placebo, which is a reasonable proxy for BSC.

For the comparison of selpercatinib versus BSC (using placebo as a proxy) in the *RET* fusion-positive TC population, the naïve comparisons demonstrate a statistically significant improvement in PFS, with a HR of [redacted] (95% CI: [redacted], [redacted]; p[redacted]), with narrow confidence intervals, equating to a [redacted]% reduction in the risk of progression for patients receiving selpercatinib versus BSC. In addition, the naïve comparisons showed a statistically significant improvement in OS, with a HR of [redacted] (95% CI: [redacted], [redacted]; p[redacted]), with narrow confidence intervals, equating to an [redacted]% reduction in the risk of death for patients receiving selpercatinib versus BSC.

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.[76] In both the *RET*-mutant MTC and *RET* fusion-positive TC populations, selpercatinib demonstrates clinically meaningful and statistically significant treatment benefits versus BSC in UK clinical practice.

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.[73]
- In the *RET*-mutant MTC SAS and the *RET* fusion-positive TC SAS, Grade 3 or 4 TEAEs were reported by 249 (76.9%) and 47 (71.2%) patients, respectively, irrespective of relatedness to selpercatinib.[74] 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.[73]
- 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).[73]

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 44 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 45 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 46. 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 44: 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),[78] Wirth *et al* (2023).[73]

Table 45: 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),[78] Wirth *et al* (2023).[73]

Table 46: 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),[78] Wirth *et al* (2023).[73]

B.2.10.2 Summary of adverse events

A summary of TEAEs observed in LIBRETTO-001 is presented in Table 47. 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 43 (13.3%) and 3 (4.5%) patients in the *RET*-mutant MTC SAS and *RET* fusion-positive TC SAS, respectively.[74] 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.[73] [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 47: 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	324 (100.0)	66 (100.0)
Related to selpercatinib	310 (95.7)	65 (98.5)
Grade ≥3 TEAE, n (%)		
All	249 (76.9)	47 (71.2)
Related to selpercatinib	139 (42.9)	24 (36.4)
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	167 (51.5)	25 (37.9)
Related to selpercatinib	43 (13.3)	3 (4.5)
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),[78] Wirth *et al* (2023),[73] Wirth *et al* (2024).[74]

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 48. 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.[73]

Table 48: 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)	16 (24.2)	[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),[78] Wirth *et al* (2023).[73]

B.2.10.3 Grade 3–4 adverse events

In the *RET*-mutant MTC SAS, Grade 3 or 4 TEAEs were reported 249 (76.9%) patients, not taking into account whether these TEAEs were related to selpercatinib treatment (Table 49).[74] The most common Grade 3–4 events were hypertension [redacted], ALT increase (9.0%), hyponatremia [redacted] and AST increase (7.7%).[73]

In the *RET* fusion-positive TC SAS, Grade 3 or 4 TEAEs were reported in 47 (71.2%) patients, irrespective of relatedness to selpercatinib, as shown by Table 49. The most common Grade 3–4 TEAEs were hypertension (15.2%), hyponatraemia [redacted] diarrhoea (7.6%) and lymphopenia [redacted].[73]

Table 49: 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),[78] Wirth *et al* (2023).[73]

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 50. 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 50: 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),[78] Wirth *et al* (2023).[73]

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 51.

Table 51: 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).[78]

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.2.11 *Ongoing studies*

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

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

Efficacy data from 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 previously received systemic therapy is informed by the LIBRETTO-001 trial. The clinical efficacy results from LIBRETTO-001 demonstrate that selpercatinib drives clinically meaningful, deep and durable responses in patients with advanced *RET*-mutant MTC and *RET* fusion-positive TC. The results presented in this submission are from the most recent 13th January 2023 DCO of the LIBRETTO-001 trial. Compared with the original appraisal in this indication (TA742) which presented data from the 16th December 2019 DCO of LIBRETTO-001, this CDF exit submission is informed by clinical data with substantially increased median duration of follow-up and greater numbers of patients in each analysis set.[3]

At the 13th January 2023 DCO, the primary endpoint in the LIBRETTO-001 trial, ORR, in the prior cabozantinib/vandetanib *RET*-mutant MTC population was 77.6% (118/152; 95% CI: 70.2, 84.0). Furthermore, 65.1% of patients experienced a PR following treatment with selpercatinib, along with 12.5% of patients experiencing a CR, demonstrating the efficacy in targeting *RET* in this patient population. Median DOR and PFS were 45.3 months and 41.4 months, respectively,

demonstrating the high rates of response achieved through treatment with selpercatinib. Furthermore, the median duration of follow-up for these endpoints (38.3 months and 44.0 months for DOR and PFS, respectively) are broadly similar to those seen in trials in similar indications.[54, 73] While median OS was reached in the prior cabozantinib/vandetanib *RET*-mutant MTC population (64.3 months), the comparatively shorter median duration of follow up for this endpoint (46.9 months) means that this result is not considered meaningful or informative.[74]

In the prior systemic therapy *RET* fusion-positive TC population, ORR was 85.4% (35/41; 95% CI: 70.8, 94.4).[74] Furthermore, 73.2% of patients experienced a PR upon treatment with selpercatinib, along with 12.2% of patients experiencing a CR. Median DOR and PFS were 26.7 months and 27.4 months, with a median follow up of 33.9 months and 30.4 months for DOR and PFS, respectively.[73] Median OS was not reached, with a median duration of follow up of 36.9 months at the DCO.[74]

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 the relevant comparator (BSC) used the best available data and methods outlined in NICE DSU TSD 18.[76]

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 and clinically meaningful treatment benefit in terms of OS and PFS when compared with placebo, a proxy for BSC (OS HR: 0.11 [95% CI: 0.07, 0.18; p<0.001]; PFS HR: 0.05 [95% CI: 0.03, 0.09; p<0.001]).

In the *RET* fusion-positive TC populations, naïve comparisons were necessary due to 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 the SELECT trial for patients receiving placebo. However, crossover-adjusted (via RPSFT) OS KM curves were available from the SELECT trial, which are expected to reduce bias associated with cross-over.

For the comparison of selpercatinib versus BSC (using placebo as a proxy) in the *RET* fusion-positive TC population, the naïve comparisons demonstrate a statistically significant improvement in PFS for patients receiving selpercatinib versus BSC, with a HR of [redacted] (95% CI: [redacted], [redacted]; p[redacted]), with narrow confidence intervals, equating to a [redacted]% reduction in the risk of progression for patients receiving selpercatinib versus BSC. In addition, the naïve comparisons showed a statistically significant improvement in OS for patients receiving selpercatinib versus BSC, with a HR of [redacted] (95% CI: [redacted], [redacted]; p[redacted]), with narrow confidence intervals, equating to an [redacted]% reduction in the risk of death for patients receiving selpercatinib versus BSC.

Safety data from LIBRETTO-001

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 249 (76.9%) and 47 (71.2%) patients, respectively, irrespective of relatedness to

selpercatinib.[74] 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.

B.3 Cost effectiveness

Cost-effectiveness model

- A 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 after cabozantinib or vandetanib' and for 'people aged 12 years and over with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib'.
- The model adopted a partitioned survival approach with three health states: progression free (PF), progressed disease (PD), and death. The model structure and inputs broadly align with the model accepted by the NICE Committee in NICE TA742, and the model currently being appraised by NICE in ID6132.[3, 67]
- Stratified and unstratified standard parametric and flexible approaches were used to extrapolate OS and PFS data for selpercatinib and best supportive care (BSC).
    - For the *RET*-mutant MTC population, the loglogistic extrapolation was selected to model PFS for selpercatinib and BSC. For OS, the stratified Weibull extrapolation was used to model selpercatinib and BSC.
    - For the *RET* fusion-positive TC population, the stratified Weibull extrapolation was selected to model PFS for selpercatinib and BSC. For OS, the piecewise exponential extrapolation was used to model selpercatinib and BSC.
    - In both populations, time to treatment discontinuation (TTD) for selpercatinib treatment was assumed equal to PFS plus an additional delay to represent the time between disease progression and treatment discontinuation based on LIBRETTO-001 trial data ([redacted] weeks for *RET*-mutant MTC and [redacted] weeks for *RET* fusion-positive TC).
    - In order to more closely align the landmark rates of OS for selpercatinib with the estimates provided by clinical experts during interviews conducted to support ID6132, an adjustment factor was applied to the selected MTC (2.0 adjustment factor) and TC (1.2 adjustment factor) selpercatinib OS curves from 5 years onwards.
- In both the *RET*-mutant MTC and the *RET* fusion-positive TC populations, patients receiving selpercatinib or BSC are assumed to receive no active subsequent treatments following disease progression. This aligns with the approach accepted in NICE TA742.[3]
- Utility values for the PF and PD health states (for both MTC and TC populations) were derived from Fordham *et al.* (2015),[96] in line with previous technology appraisals (TA516, TA535 and TA721).[3, 26, 27]
- 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).[26, 27]
- As above, feedback from UK clinicians to support the appraisal for selpercatinib in untreated advanced thyroid cancer with *RET* alterations (ID6132) was used to validate the assumptions and inputs included in the model.[69]

Comparators

- For patients with *RET*-mutant MTC, selpercatinib was compared to BSC via a matching-adjusted indirect comparison (MAIC) which used data from the LIBRETTO-001 trial for selpercatinib survival inputs, and the EXAM trial for BSC survival inputs.[54, 91]
- For patients with *RET* fusion-positive TC, selpercatinib was compared to BSC via a naïve indirect treatment comparison (ITC) which used data from the LIBRETTO-001 trial for selpercatinib survival inputs and the SELECT trial for BSC survival inputs.[55]
- Whilst efficacy data for selpercatinib are available from LIBRETTO-001 for patients with TC and MTC who had received prior systemic therapy, combined data from the any-line *RET*-altered TC and MTC populations were used to more closely align with the BSC 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 relevance 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 an ICER of £47,795 per QALY gained versus BSC; however, selpercatinib is eligible for a 1.2x severity modifier versus BSC, and these results do not include the 1.2x severity modifier.
- For advanced *RET*-fusion TC selpercatinib was associated with an ICER of £45,120 per QALY gained versus BSC; however, selpercatinib is eligible for a 1.2x severity modifier versus BSC, these results do not include the 1.2x severity modifier.

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 deterministic sensitivity analysis (DSA) were the discount rate (costs and outcomes), the progression-free health state utility value and the progression-free health state 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 ~£2,000/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 thus 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 G.

As TC and MTC are rare types of cancer and there are no other selective *RET* kinase inhibitors currently available to patients who have 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. The original TLR was conducted in advance of TA742, with a subsequent targeted update carried out to capture any relevant NICE TAs published after TA742, the original appraisal for selpercatinib for treating advanced thyroid cancer with *RET* alterations.

Six appraisals in thyroid cancer indications were identified as part of the TLR:

- Cabozantinib for treating MTC (TA516)[26]
- Vandetanib for treating MTC (TA550)[65]
- Lenvatinib and sorafenib for treating DTC after radioactive iodine (TA535)[27]
- Selpercatinib for treating advanced *RET*-mutant MTC and *RET*-fusion positive TC (TA742)[3]
- Cabozantinib for previously treated differentiated TC (TA928)[66]

- Selpercatinib for untreated advanced thyroid cancer with *RET* alterations (ID6132)[67]

Of these appraisals, TA742, the original appraisal for selpercatinib for treating advanced thyroid cancer with *RET* alterations, is considered the most relevant appraisal for this submission. ID6132, the ongoing appraisal for selpercatinib in first-line advanced RET-altered thyroid cancer, as well as TA516, TA535, are also considered relevant, however these appraisals all considered patients populations that had not previously received systemic therapy. A summary of these appraisals is provided in Table 52.

TA550 and TA928 received negative recommendations from NICE. Despite the negative recommendation, TA928 is also considered relevant to this submission as the most recent appraisal in second-line thyroid cancer, providing insight into preferred assumptions and inputs for the cost-effectiveness model as detailed throughout Section B.3.

Table 52: 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)
TA742 (2021), UK, CUA	• Advanced *RET* fusion-positive TC in adults who require systemic therapy after sorafenib or lenvatinib • Advanced *RET*-mutant medullary thyroid cancer in people 12 years and older who require systemic therapy after cabozantinib or vandetanib	• **Model type:** Partitioned survival model • **Health states:** 3 (progression-free, progressed and death) • **Cycle length:** Weekly • **Discount rate:** 3.5% and half cycle correction • **Time horizon:** 25 years (lifetime)	***RET*-mutant MTC** • [redacted] versus [redacted] (Selpercatinib, Cabozantinib) • [redacted] versus [redacted] (Selpercatinib, BSC) ***RET* fusion-positive TC** • [redacted] versus [redacted] (Selpercatinib, BSC)	***RET*-mutant MTC** • £[redacted] versus £[redacted] (Selpercatinib, Cabozantinib) • £[redacted] versus £[redacted] (Selpercatinib, BSC) ***RET* fusion-positive TC** • £[redacted] versus £[redacted] (Selpercatinib, BSC)	***RET*-mutant MTC** • £[redacted] (Selpercatinib, Cabozantinib) • £[redacted] (Selpercatinib, BSC) ***RET* fusion-positive TC** • £[redacted] (Selpercatinib, BSC)
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	• **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	• 2.82 versus 1.60 (Lenvatinib, BSC)	• £95,102 versus £15,195 • (Lenvatinib, BSC)	• £65,872

	• 0 or 1 prior VEGF/VEGFR therapy • ECOG 0-2	correction • **Time horizon:** 33 years (scenarios: 5 and 10 year)			
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
ID6132 (2023), UK, CUA	• Advanced *RET* fusion-positive TC in in people aged 12 years and older who require systemic therapy (and who have not previously received systemic therapy) • Advanced *RET*-mutant medullary thyroid cancer in people aged 12 years and older who require systemic therapy (and who have not previously received systemic therapy)	• **Model type:** Partitioned survival model • **Health states:** 3 (progression-free, progressed and death) • **Cycle length:** Weekly • **Discount rate:** 3.5% and half cycle correction • **Time horizon:** 35 years (lifetime)	***RET*-mutant MTC[a]** • [redacted] versus 2.11 (Selpercatinib, Cabozantinib) • [redacted] versus 1.52 (Selpercatinib, BSC) ***RET* fusion-positive TC** • [redacted] versus 2.63 (Selpercatinib, Lenvatinib) • [redacted] versus 1.28 (Selpercatinib, BSC)	***RET*-mutant MTC[a]** • £[redacted] versus £89,785 (Selpercatinib, Cabozantinib) • £[redacted] versus £17,110 (Selpercatinib, BSC) ***RET* fusion-positive TC** • £[redacted] versus £96,510 (Selpercatinib, Lenvatinib) • £[redacted] versus £15,983 (Selpercatinib, BSC)	***RET*-mutant MTC[a]** • £35,852 (Selpercatinib, Cabozantinib) • £47,349 (Selpercatinib, BSC) ***RET* fusion-positive TC** • £36,347 (Selpercatinib, Lenvatinib) • £44,429 (Selpercatinib, BSC)

[a] The values presented represent the base case results following clarification questions for the ongoing appraisal ID6132.

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,[26] NICE TA535,[27] NICE TA742,[3] NICE ID6132.[67]

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 previously received systemic therapy for advanced disease.

A cost-effectiveness analysis of selpercatinib versus the relevant comparator, BSC, as per 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 after cabozantinib and/or vandetanib
- People aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib and/or lenvatinib

These populations reflect the current positioning of selpercatinib within the CDF in UK clinical practice and the anticipated positioning of selpercatinib if approved for routine commissioning in UK clinical practice. UK clinical experts validated this pathway as representative of UK clinical practice during interviews conducted to support prior NICE appraisals of selpercatinib as a treatment for advanced *RET*-altered thyroid cancer, TA742 (advanced *RET*-altered thyroid cancer in patients who had previously received systemic treatment) and NICE ID6132 (advanced *RET*-altered thyroid cancer in patients who have not previously received systemic treatment).[42, 69]

As highlighted 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" as this submission covers only those patients with MTC who require systemic therapy and who have previously received systemic therapy.[1]

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).[73, 80] 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 BSC.[54]

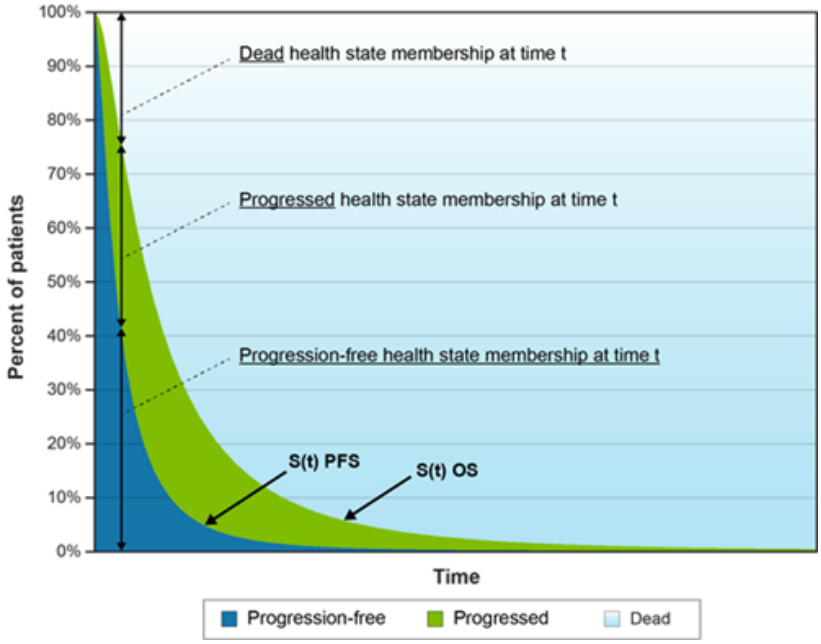
As highlighted in Section B.1.1, the *RET* fusion-positive TC population of relevance to this submission is also narrower than the technology's full anticipated marketing authorisation for selpercatinib "as monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET* fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate)", as this submission covers only those patients aged 12 years and older with TC who require systemic therapy who have previously received systemic therapy.

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).[73, 80] 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 BSC.

B.3.2.2 Model structure

An economic model was developed in Microsoft Excel to evaluate the cost-effectiveness of selpercatinib versus BSC, the relevant comparator in UK clinical practice in the populations of interest to this submission. A cohort-based partitioned survival model (PSM) was developed, consisting of three mutually exclusive health states: PF, PD and death. A graphical depiction of the PSM structure is presented in Figure 32.

Figure 32: 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 comparator, BSC, 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, TA742 and ID6132).[3, 26, 27, 67]

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 BSC. The proportion of patients in each heath state at each weekly 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 analysis

The economic analysis for this evaluation was compared to previous NICE evaluations in advanced TC and MTC. Table 53 summarises the features of the economic analyses used in the previous selpercatinib appraisal for advanced *RET*-altered MTC and TC for patients who have previously received systemic therapy (TA742), as well as the models utilised for the prior appraisals for advanced MTC and TC for patients who have not previously received systemic therapy (TA516 and TA535), with justification provided on the approach taken for the current analysis.[3, 26, 27]

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, 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 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 35 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.[97]

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 and/or converted to UK, as applicable.[98]

Table 53: 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 (35 years)	NICE reference case[97]
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[97]
Source of utilities	Fordham *et al.* (2015)[96] PF state: 0.80 PD state: 0.50 Disutility AEs: −0.11	Fordham *et al.* (2015)[96], DECISION trial[94] **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)[96] PF state: 0.80 PD state: 0.50 Disutility AEs: −0.11	Fordham *et al.* (2015)[96] PF state: 0.80 PD state: 0.50 Disutility AEs: Various (Table 74 and Table 75)	Health-state utility estimates reported by Fordham *et al*. (2015)[96] were accepted by the NICE appraisal committee in TA516, TA535 and TA742.[3, 26, 27] 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, which were associated with uncertainty due to small patient numbers (especially in the PD health state). These findings are in line with the findings during the original NICE submission, TA742.[1]

		Sorafenib SD state: 0.68 Responsive state: 0.74 Progressive state: 0.64			Given this, and that no novel utility data were identified as part of the SLRs, the use of utilities from Fordham *et al.* (2015)[96] was considered to represent the most appropriate 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[26, 27, 97]
Resource use	Expert opinion	Expert opinion	Resource use was derived from prior appraisals[26, 27]	Resource use was derived from prior appraisals[26, 27]	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[97]

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) 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]

Comparator: *RET*-mutant MTC

In line with the current routinely available treatment in UK clinical practice, the comparator included in the model for the *RET*-mutant MTC population was BSC (Section B.1.1). 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 and TA742 and also discussed in Section B.2.9.1.[3, 26]

Comparator: *RET*-fusion positive TC

In line with the current routinely available treatment in UK clinical practice, the comparator included in the model for the *RET* fusion-positive TC population was BSC (Section B.1.1). 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.2.9.2, the placebo arm in the SELECT trial (investigating lenvatinib versus placebo) was considered to represent a suitable proxy for BSC; this is aligned with TA535 and TA742.[3, 27] Whilst the SELECT trial only included patients with DTC, the placebo arm of the trial was 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) since patients with other subtypes of TC have no suitable treatment options other than BSC.

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.[78] For BSC, clinical data in *RET*-mutant MTC were derived from the EXAM trial,[54, 91, 92] while in *RET*-fusion positive TC clinical data were derived from the SELECT trial.[55]

RET-mutant MTC

As discussed in Section B.2.9.1, 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

patients in total) and summary evidence from the EXAM trial, as reported in Schlumberger *et al.*(2017) and Sherman *et al.* (2016).[54, 80, 92] The any-line *RET*-mutant pooled population from the LIBRETT0-001 trial was used rather than the prior cabozantinib/vandetanib *RET*-mutant population (MTC: Cab/Van) 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, as patient characteristics for a *RET*-mutant subgroup treated with placebo in the EXAM trial were not available.

A summary of the clinical evidence sources informing parameters for selpercatinib and BSC for patients with *RET*-mutant MTC in the economic model is provided in Table 54.

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 treated with placebo (n=45) of the EXAM trial.[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]

Table 54: Summary of clinical evidence sources informing parameters for selpercatinib and BSCs in the economic model (*RET*-mutant MTC population)

Clinical parameter	Intervention and comparators	
	Selpercatinib[73, 80]	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 placebo (n=62) in the EXAM trial, from Sherman *et al.* (2016)[92]
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	• 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 prior cabozantinib/vandetanib *RET*-mutant MTC population in LIBRETTO-001 ([redacted] weeks)	NA
AEs	• LIBRETTO-001 MTC SAS (n=324)	• Placebo arm of the EXAM trial (n=109), from Elisei *et al.* (2013)[91]

Abbreviations: AEs: adverse events; BSC: best supportive care; Cab: cabozantinib; KM: Kaplan-Meier; MTC: medullary thyroid cancer; NA: not applicable; 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.2.9.2, 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 placebo (as a proxy for BSC). As discussed in Section B.2.9.2, 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, TA742 and ID6132.[3, 27, 67]

The clinical evidence sources informing parameters for selpercatinib and BSC for patients with *RET* fusion-positive TC in the economic model are summarised in Table 55. KM data for 131 patients who received placebo from the SELECT ITT population (Section B.2.9.2) were used in the economic model to estimate PFS for BSC for the *RET* fusion-positive TC population. OS for BSC in the model was based on rank preserving structural failure time (RPSFT)-adjusted OS data for patients receiving placebo in the ITT population.

Table 55: Summary of clinical evidence sources informing parameters for selpercatinib and BSC in the economic model (*RET* fusion-positive TC population)

Clinical parameter	Intervention and comparators	
	Selpercatinib[73, 80]	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 placebo (n=131) in SELECT, from Schlumberger *et al.* (2015)[55]
OS	• KM data for LIBRETTO-001 any-line population (n=65)	• RPSFT-adjusted KM data for patients receiving placebo (n=131) in the ITT population of SELECT, from NICE TA535[27]
Time-on-treatment	• Assumed equal to PFS with an additional delay based on the delay between disease progression and treatment discontinuation observed in the prior systemic therapy *RET* fusion-positive TC population in LIBRETTO-001 ([redacted] weeks)	NA
AEs	• LIBRETTO-001 TC safety analysis set (n=66)	• Placebo arm of the SELECT trial (n=131); Schlumberger *et al.* (2015)[55]

[a] Comprised of the 'TC: TrtSysNaïve' population (N=24) and the 'TC: TrtSys' population (patients with *RET* fusion-positive TC who had received prior systemic therapy) (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; NA: not applicable; 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 56. Mean age and the percentage of females 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 56: 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,[78] Raez *et al* (2023).[80]

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, EXAM, and SELECT) were shorter than the model time horizon (Section B.3.2.2), extrapolation from the observed OS and PFS data was required. [27, 54, 55, 78, 91, 92]

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.[99]

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.[100] For the spline models, these were developed based on the algorithm by Royston and Parmar *et al.* (2002).[101] 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:[100]

- 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 TA742 for selpercatinib[3, 26, 27]
    - Feedback from UK clinical experts was gathered as part of the ongoing appraisal for selpercatinib in advanced untreated thyroid cancer with *RET* alterations (ID6132), which also used the any-line TC and MTC LIBRETTO-001 populations to inform the economic model. As part of this clinical validation, teleconference interviews were conducted to determine plausible long-term estimates of PFS and OS for selpercatinib and BSC. When curves were being selected to extrapolate 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) in the EXAM trial.

The AIC and BIC values for each survival model are presented in Table 57, and the long-term extrapolations of PFS are presented in Figure 33 and Figure 34. Table 58 and Table 59 present the corresponding median and landmark PFS estimates (at 5, 10 and 20 years). The results of proportional hazards assessments for selpercatinib versus BSC in the *RET*-mutant MTC population are presented in Appendix N.1.

As part of the clinical validation interviews conducted to support ongoing appraisal ID6132, plausible long-term estimates of PFS and OS for selpercatinib and BSC in patients with advanced *RET*-altered thyroid cancer were elicited from clinical experts in thyroid cancer.[69] These estimates are provided in the mean and landmark estimates tables (PFS and OS) for selpercatinib and BSC, below.

Table 57: Summary of goodness-of-fit data for stratified models for progression-free survival for selpercatinib 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; NA: not applicable.

Figure 33: 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 58: 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 34: 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 59: 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.

During interviews to support the ongoing selpercatinib appraisal in untreated advanced thyroid cancer with *RET* alterations (ID6132), UK clinical experts provided estimates of the proportion of patients anticipated to be progression-free following treatment with each treatment at landmark timepoints.[69] Based on these estimates, the loglogistic extrapolation was selected to model PFS for selpercatinib and BSC. This also aligns with the preferences of the Committee in the original appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742), which was based on an earlier data cut of the same populations of LIBRETTO-001 used to inform the efficacy of selpercatinib and BSC in this appraisal.[3]

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 selpercatinib and placebo 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 N. A range of parametric functions were fitted to the weighted OS curves for selpercatinib generated in the MAIC and the unweighted OS curve for the *RET* M918T-positive subgroup receiving placebo (n=45) in the EXAM trial.

Table 60 summarises the AIC and BIC values for each survival model, and the long-term extrapolations of OS are presented in Figure 35 and Figure 36. Table 61 and Table 62 present the corresponding median and landmark OS estimates (at 5, 10 and 20 years).

Table 60: Summary of goodness-of-fit data for selpercatinib 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 35: Extrapolations of OS – Selpercatinib, *RET*-mutant MTC

[redacted]

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

Table 61: 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]
Median and landmark survival with adjustment factor applied				
Stratified Weibull (2.0 adjustment factor)	[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 36: 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 62: 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.

As outlined above, to support the ongoing appraisal for selpercatinib in untreated, advanced thyroid cancer with *RET* alterations (ID6132), UK clinical experts provided estimates of the proportion of patients anticipated to be alive following treatment with each selpercatinib and BSC at landmark timepoints.[69] Based on these estimates, the stratified Weibull extrapolation was selected to model OS for selpercatinib and BSC; 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 the original appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742) for patients previously treated with systemic therapy, which was based on an earlier data cut of the same populations of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal.[3]

Despite the stratified Weibull aligning most closely with the estimates provided by the UK clinical experts during ID6132, the landmark estimates for OS for selpercatinib based on this curve overestimate survival versus these estimates. In order to more closely align selpercatinib OS with the plausible range provided by the clinical experts at 10 and 20 years, an adjustment factor of 2.0 was applied to the selpercatinib OS curve in the *RET*-mutant MTC population from five years and onwards, as presented in Table 61.

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. For the *RET*-mutant MTC population, the adjustment factor is set to 2.0 and is applied from five years onwards. Further information on the application of the adjustment factor in the model are provided in Appendix O. Once the 2.0 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).

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 BSC with no adjustment factor applied.

Based on the stratified Weibull extrapolation with the 2.0 adjustment factor applied, 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 35 years, thereby decreasing any uncertainty associated with the long-term extrapolation of selpercatinib OS.

The stratified gamma extrapolation was explored in a scenario analysis, also applying the 2.0 adjustment factor.

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 N. 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 BSC (n=131).

Table 63 summarises the AIC and BIC values for the best-fitting survival models, and the long-term extrapolations of PFS are presented in Figure 37 and Figure 38 for selpercatinib and BSC, respectively. Table 64 and Table 65 present the corresponding median and landmark PFS estimates (at 5, 10 and 20 years) for selpercatinib and BSC, respectively.

Table 63: Summary of goodness-of-fit data for selpercatinib 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 37: Extrapolations of PFS – Selpercatinib, *RET* fusion-positive TC

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

Table 64: 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: NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection; TC: thyroid cancer.

Figure 38: 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 65: 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; NA: not applicable; 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.[27] 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.

As outlined previously, to support the ongoing appraisal for selpercatinib in untreated, advanced thyroid cancer with *RET* alterations (ID6132), UK clinical experts provided estimates of the proportion of patients anticipated to be progression-free following treatment with selpercatinib and BSC at landmark timepoints.[69] Based on these estimates, the stratified Weibull extrapolation was selected to model PFS for selpercatinib and BSC; the selection of the same extrapolation to model PFS for selpercatinib and BSC is in line with guidance from NICE DSU.[9]

The selection of the stratified Weibull curve also aligns with the preferences of the Committee in the original appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742), which was based on an earlier data cut of the same populations of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal.[3]

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 N. 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 placebo from the SELECT trial.

Table 66 summarises the AIC and BIC values for each survival models, and the long-term extrapolations of OS are presented in Figure 39 and Figure 40 for selpercatinib and BSC, respectively. Table 67 and Table 68 present the corresponding median and landmark OS estimates (at 5, 10 and 20 years) for selpercatinib and BSC, respectively.

Table 66: Summary of goodness-of-fit data for selpercatinib 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 39: Extrapolations of OS – Selpercatinib, *RET* fusion-positive TC

[redacted]

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

Table 67: 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]
Median and landmark survival with adjustment factor applied				
Piecewise exponential (1.2 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: NA: not applicable; OS: overall survival; *RET*: rearranged during transfection; TC: thyroid cancer.

Figure 40: 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 68: 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; NA: not applicable; 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 the ongoing appraisal for selpercatinib in untreated, advanced thyroid cancer with *RET* alterations (ID6132), UK clinical experts provided estimates of the proportion of patients anticipated to be alive following treatment with each treatment at landmark timepoints.[69] Based on these estimates, the piecewise exponential extrapolation was selected to model OS for selpercatinib and BSC.

This extrapolation also aligns with the preferences of the Committee in the original appraisal of selpercatinib in advanced *RET*-altered TC and MTC for patients who had received a prior systemic therapy (TA742), which was based on an earlier data cut of the same populations of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal, as well as TA535.[3, 27]

Despite the OS landmark estimates for the piecewise exponential extrapolation survival broadly aligning with the UK clinical expert estimates, an adjustment factor of 1.2 was applied from 5 years and onwards, to ensure that the estimated landmark rates of OS fell within the range provided by UK clinical experts, particularly at 10 years, as presented in Table 67. The adjustment factor was applied in the same way as described in Section B.3.3.3 and Appendix O.

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

The Weibull extrapolation, with the 1.2 adjustment factor applied, 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.[78] During interviews conducted to support the ongoing appraisal for selpercatinib in untreated, advanced thyroid cancer with *RET* alterations (ID6132), UK clinical experts stated that patients may remain on active 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.[69]

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 prior

cabozantinib/vandetanib *RET*-mutant MTC and the prior systemic therapy *RET* fusion-positive TC populations ([redacted] weeks for MTC and [redacted] weeks for TC). This approach is aligned with the EAG's preferred approach in the original appraisal of selpercatinib in the indications of interest, TA742.[3]

TTD is not considered in the economic model for BSC, as there are no specific costs associated with BSC beyond the palliative care and monitoring costs discussed in Section B.3.5.1.

After discontinuation all patients are assumed to not receive any subsequent treatments. This is aligned with the approach accepted in the original appraisal of selpercatinib for patients with advanced *RET*-altered thyroid cancer that have received prior systemic therapy, TA742.[3] During clinical validation conducted to support TA742, a UK clinical expert supported that a patient with advanced, *RET*-altered TC or MTC experiencing disease progression on selpercatinib would have no further treatment options.[42] This is further supported by feedback collected from UK clinical experts as part of ID6132, who stated 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, and that patients receiving BSC would not receive an active treatment following disease progression.[69]

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 69 and Table 70 for the *RET*-mutant MTC and *RET* fusion-positive TC populations, respectively.

Table 69: Summary of selected base case survival approaches – *RET*-mutant MTC

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

[a] An adjustment factor of 2.0 was applied to the selpercatinib OS curves from 5 years onwards.
Abbreviations: BSC: best supportive care; HR: hazard ratio; NA: not applicable; OS: overall survival; NA: not applicable; PFS: progression-free survival; TTD: time to treatment discontinuation.

Table 70: Summary of selected base case survival approaches – *RET* fusion-positive TC

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

[a] An adjustment factor of 1.2 was applied to the selpercatinib OS curves from 5 years onwards.
Abbreviations: BSC: best supportive care; HR: hazard ratio; NA: not applicable; OS: overall survival; NA: not applicable; 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, TA535 and ID6132.[26, 27, 67] The AEs included for each treatment arm for the *RET*-mutant MTC and *RET* fusion-positive TC populations are presented in Table 71 and Table 72, 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 BSC in *RET*-mutant MTC were taken from the EXAM trial.[54, 91]

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 BSC in *RET* fusion-positive TC were taken from SELECT.[55]

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

Adverse event	Selpercatinib (n=324)	BSC (n=109)
Diarrhoea	6.79%	1.83%
Hypertension	21.60%	0.00%
ECG QT prolonged	[redacted]	0.00%
Decreased weight	[redacted]	0.00%
Abdominal pain	3.09%	0.92%
Haemorrhage	[redacted]	0.92%
Dysphagia	[redacted]	0.92%
Fatigue	3.70%	2.75%
Decreased appetite	[redacted]	0.92%
Asthenia	[redacted]	1.83%
Dyspnoea	[redacted]	0.00%
Headache	2.78%	10.09%
Back pain	[redacted]	0.92%
Alanine aminotransferase increased	8.95%	1.83%
Aspartate aminotransferase increased	7.72%	0.00%
Hyponatraemia	[redacted]	0.00%
Lymphopenia	[redacted]	10.09%
Pneumonia	[redacted]	0.00%
Hypocalcaemia	5.25%	0.00%
Dehydration	[redacted]	0.00%
Weight increased	[redacted]	0.00%
Ascites	[redacted]	0.00%
Sepsis	[redacted]	0.00%
Hyperkalaemia	[redacted]	0.00%
Hypophosphatemia	[redacted]	0.00%
Hyperglycaemia	[redacted]	0.00%
Hypercalcemia	[redacted]	0.00%
Source	LIBRETTO-001, MTC safety analysis set (n=324)	EXAM[54, 91]

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

Table 72: Incidence of Grade 3 or 4 adverse events included in the model for the *RET* fusion-positive TC population

Adverse event	Selpercatinib (n=66)	BSC (n=131)
Diarrhoea	7.58%	0.00%
Hypertension	15.15%	3.82%
ECG QT prolonged	[redacted]	0.00%
Decreased weight	[redacted]	0.76%

Abdominal pain	[redacted]	0.00%
Sepsis	[redacted]	0.00%
Dysphagia	[redacted]	3.05%
Fatigue	1.52%	1.53%
Decreased appetite	1.52%	0.76%
Asthenia	[redacted]	2.29%
Hyponatraemia	[redacted]	0.00%
Vomiting	[redacted]	0.00%
Dyspnoea	[redacted]	3.05%
Headache	[redacted]	0.76%
Back pain	3.03%	0.00%
Hypophosphatemia	[redacted]	0.00%
Alanine aminotransferase increased	[redacted]	0.00%
Aspartate aminotransferase increased	[redacted]	0.00%
Thrombocytopenia	[redacted]	0.00%
Lymphopenia	[redacted]	0.00%
Pneumonia	[redacted]	0.00%
Hypocalcaemia	[redacted]	0.00%
Anaemia	[redacted]	0.00%
Hypokalaemia	[redacted]	0.00%
Leukopenia	[redacted]	0.00%
Nausea	0.00%	0.76%
Stomatitis	[redacted]	0.00%
Neutropenia	[redacted]	0.00%
Confused state	[redacted]	0.00%
Source	LIBRETTO-001, TC safety analysis set (n=66)	SELECT[27]

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 original appraisal for selpercatinib in the indications of interest, NICE TA742,[3] 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 elected for the use of utility values that were the same as those used in TA516,[26] and TA535,[27] sourced from a vignette study conducted by Fordham *et al* (2015).[96]

For completeness, the updated EORTC-QLQ-C30 data from the any-line *RET*-altered TC and MTC populations from the 13th 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).[102-104] The results are presented in Table 73.

In both the any-line MTC and TC populations, the mapped utility estimates remain implausible. 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 associated with substantial uncertainty due to small patient numbers and number of assessments (particularly in the progressed disease health state, where N=[redacted] with a total of [redacted] assessments). Furthermore, the utility estimates remain implausible as the similarity between the progression-free and progressed disease mapped utilities estimates does not reflect the anticipated loss in HRQoL associated with disease progression.

Table 73: 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[c]		
EORTC-8D	[redacted]	[redacted]
Mapped to EQ-5D (Young 2015)[e]	[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] *RET* fusion-positive MTC (any-line population). [d] All post-baseline pre-progression assessments. [e] 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,[105] Lilly data on file, 2023,[78], Young *et al*. (2015),[102] Marriott *et al*. (2017),[104] Kontodimopoulos *et al*. (2009).[103]

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

As direct elicitation of utilities was not possible and mapping of disease-specific measures of health status collected in LIBRETTO-001 produced implausible results, 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 addition, in the SLR conducted as part of TA928, no additional relevant HRQoL or utility data were identified.[66]

Therefore, 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).[3, 26, 27, 96]

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 74 and Table 75. 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,[26] TA535,[27] and TA742,[3] all AEs were assumed to have a duration of one month (30.44 days).

Table 74: 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. [106]
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	
Asthenia	−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[26]

Table 75 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
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
Abdominal pain	−0.110	NICE TA516	30.4	NICE TA535
Sepsis	−0.110	NICE TA516	30.4	NICE TA535
Dysphagia	−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
Asthenia	−0.110	NICE TA516	30.4	NICE TA535
Hyponatraemia	−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
Hypophosphatemia	−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
Anaemia	−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

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[26]; NICE TA535[27]

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.[3] 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 and uncertain due to small patient numbers for the MTC and TC populations. 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), which were accepted by the NICE Committee in TA516, TA535, and TA742, were used in base case analysis of the model and are presented in Table 76.[3, 26, 27, 96] The same utility values were also preferred by the NICE Committee in TA928 when the utility values derived from the pivotal clinical trial were deemed to be not robust or clinically plausible.[66] 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),[96] 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.[42]

Table 76: Health-state utility estimates in DTC by Fordham et al. (2015)[96]

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

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

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).[107]

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.[3] Relevant resource use and costs were extracted from TA516 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.[3, 26, 27]

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 77 presents the drug acquisition costs for selpercatinib based on the current list price and licensed dose. The economic model also accounts for patients that require dose modifications, with Table 78 presenting the relative dose intensity for selpercatinib.

The proportion of selpercatinib administrations at each dose level was based on the recorded doses received in the LIBRETTO-001 trial (Table 79), 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 SAS; [redacted]% for *RET* fusion-positive TC SAS). The proportion of patients receiving each dose of selpercatinib in the model are provided in Table 79. This approach is in

line with that accepted in TA742, and was also adopted in ID6132, the ongoing appraisal for first-line selpercatinib in *RET*-altered thyroid cancer.[3, 67]

The total costs for selpercatinib are derived by applying the drug acquisition costs to the modelled TTD, as described in Section B.3.3.5.

Table 77: Drug acquisition costs for selpercatinib

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]

One pack size is presented for each drug in the table above.
Abbreviations: BNF: British National Formulary; PAS: Patient Access Scheme.
Source: List prices for each treatment are sourced from the BNF.[108]

Table 78: Relative dose intensity for selpercatinib

Regimen	*RET*-mutant MTC	*RET* fusion-positive TC	Source
Selpercatinib[a]	[redacted]	[redacted]	Lilly data on file, LIBRETTO-001

[a] These data are not used for selpercatinib in the first cycle of 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[78]

Table 79: 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, 12 minutes of pharmacy time (£11.40) was assumed every 30 days.[109] This is aligned with the approach accepted as part of TA742.

In addition, the costs of seven 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.[3, 26] The costs and resource use frequency assumed in the base case are presented in Table 80.

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.[3]

Table 80: Unit costs and resource use per year in *RET*-mutant MTC and *RET*-fusion positive TC populations

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[26]

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 81). These costs are based on the data used in the Assessment Group and Sanofi model in TA516 which were, in turn, derived from the NHS Reference Costs and the Personal Social Services Research Unit (PSSRU), which is consistent with NICE TA742.[3, 26]

Table 81: 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[26]

Subsequent treatments

Following disease progression, patients receiving selpercatinib or BSC are assumed to receive no active subsequent treatments, as no subsequent treatments are available following treatment with second-line selpercatinib or BSC. This approach is aligned with that used in TA742 and is

also supported by feedback from UK clinical experts collected to support TA742 and ID6132.[3, 42, 69]

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs for adverse events are presented in Table 82 and Table 83. Costs were taken from NHS Reference Costs (2021/22; where available), based on the cost codes used as part of TA516 and TA742.[3, 26]

Table 82: 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)
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)
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
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[26]

Table 83: 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)
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)
Sepsis	5,779.96	NHS Reference costs 2021/22 (WJ06D-F Sepsis with Single Intervention, with CC Score 0-9+; Non-Elective inpatient)
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)
Asthenia	0.00	Assumption
Hyponatraemia	0.00	Assumption
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)
Hypophosphatemia	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)
Anaemia	0.00	Assumption
Leukopenia	0.00	Assumption
Nausea	0.00	Assumption
Stomatitis	0.00	Assumption
Neutropenia	0.00	Assumption
Confused state	0.00	Assumption

Abbreviations: ECG: electrocardiogram.
Source: NICE TA516[26]

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.[8, 9] 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).[3]

However, in line with the Committee's preferences in the evaluation of selpercatinib as a treatment for *RET* fusion-positive NSCLC (TA911) and the original evaluation for selpercatinib in second-line thyroid cancer (TA742), 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 84.

Table 84: 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)[110] and Wells et al. (2015)[24]*	6.8% *Source: Liu et al., 2014[111]*
RET test cost	£34 *Source: TA911[4]*	

[a] Wells *et al.* (2015)[24] reported that 50% of sporadic MTCs and 95% of hereditary MTCs have *RET* mutations. Taccaliti *et al.* (2011)[110] 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.[112] A summary of the features of the QALY shortfall analysis is provided in Table 85. In line with the NICE reference case, the Hernandez-Alava 2017 study, which mapped the EQ-5D-5L to the 3L, was used (Table 86).[113, 114]

The results demonstrate that for the *RET*-mutant MTC population, selpercatinib is eligible for a 1.2x severity modifier when compared with BSC. In the *RET*-fusion positive TC population, selpercatinib is eligible for a 1.2x severity modifier when compared with BSC (Table 86).

Table 85: 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 (% female)	39.0%	Section B.3.3.1, Table 56
Starting age (mean)	[redacted]	Section B.3.3.1, Table 56
Health state utility: PF	0.80	Section B.3.4.5, Table 76
Health state utility: PD	0.50	Section B.3.4.5, Table 76
***RET*-fusion Positive TC**		
Sex distribution (% female)	50.8%	Section B.3.3.1, Table 56
Starting age	[redacted]	Section B.3.3.1, Table 56
Health state utility: PF	0.80	Section B.3.4.5, Table 76
Health state utility: PD	0.50	Section B.3.4.5, Table 76

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

Table 86: Summary of QALY shortfall

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**				
14.02	1.51	14.02	89.23%	1.2
***RET*-fusion positive TC**				
13.39	1.27	12.12	90.51%	1.2

Abbreviations: QALY: quality-adjusted life year; MTC: medullary thyroid cancer; TC: thyroid cancer.

B.3.7 *Uncertainty*

Due to the rarity of advanced *RET*-altered thyroid cancer, 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 BSC. 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 prognostic influence of *RET* alterations remains unclear.[41, 42]

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. This means that 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 BSC, as further outlined in Section B.2.9.2. Nevertheless, this approach is in line with that accepted in previous NICE evaluations of selpercatinib, including TA742.[3]

In addition, efficacy data for BSC from EXAM or SELECT were not available for the endpoints of interest for subpopulations of patients who had received previous systemic treatment for advanced disease. As such, it was necessary to use line-agnostic data for both BSC and selpercatinib; in the ITCs, the efficacy of selpercatinib is informed by the any-line cohorts 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 populations, when compared with the treatment-experienced populations, results in increased robustness and precision of the comparative efficacy estimates. The use of the any-line populations for MTC and TC will slightly overestimate OS and PFS for selpercatinib, compared with the prior systemic therapy population for MTC and TC, which represent the populations of interest for this submission. However, this was required due to the absence of published data for endpoints of interest for a prior systemic therapy population from EXAM or SELECT to inform the efficacy of BSC. As such, any-line populations were also used to inform the efficacy of the comparators, so this is not expected to be a significant source of bias in the ITCs.

The data for OS from LIBRETTO-001 are 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 the ongoing appraisal for selpercatinib in advanced, untreated thyroid cancer with *RET* alterations (ID6132)

regarding the anticipated long-term survival for patients with *RET*-altered MTC and TC treated with selpercatinib.[69] Additionally, validation of long-term extrapolations was conducted with UK-based clinical experts as part of the original appraisal of selpercatinib in advanced *RET*-altered TC and MTC (TA742) for patients previously treated with systemic therapy.[3] 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 populations as part of TA742, providing further confidence in the modelled survival estimates.

B.3.8 *Managed access proposal*

N/A – this appraisal is assessing the cost-effectiveness of selpercatinib in order to transition from use within the CDF to routine commissioning in UK clinical practice.

B.3.9 *Summary of base-case analysis inputs*

A summary of inputs for the base case analysis is presented in Table 87.

Table 87: 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 (35 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 (BSC)			
OS (selpercatinib)	Stratified Weibull (2.0 adjustment factor applied from Year 5)	Piecewise exponential (1.2 adjustment factor applied from Year 5)	
OS (BSC)	Stratified Weibull	Piecewise exponential	
TTD (selpercatinib)	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 71	Table 72	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 74	Table 75	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]		
Administration cost per treatment cycle (all treatments)	£11.40		
ECG cost (selpercatinib only)	£159.36		
Mean RDI (selpercatinib for *RET*-mutant MTC)	[redacted]		
PF average resource use frequencies	Table 80		Section B.3.5.2
PD average resource use frequencies	Table 80		
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 82	Table 83	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 88, 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 93.

Table 88: Modelling assumptions

Parameter	Assumption	Justification	Addressed in scenario analysis
Survival models			
PFS curves	*RET*-mutant MTC: loglogistic (both treatment arms) *RET* fusion-positive TC: stratified Weibull (both 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 both treatment arms).
OS curves	*RET*-mutant MTC: stratified Weibull (both treatment arms; 2.0 adjustment factor applied to selpercatinib OS after 5 years) *RET* fusion-positive TC: piecewise exponential (both treatment arms; 1.2 adjustment factor applied to selpercatinib OS after 5 years)	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 as part of the ongoing appraisal for selpercatinib in advanced untreated thyroid cancer with RET alterations (ID6132).[67] 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 both treatment arms).
TTD	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks and [redacted] weeks applied to selpercatinib in the prior treatment *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 prior cabozantinib/vandetanib *RET*-mutant MTC population and the prior systemic therapy *RET* fusion-positive 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	A scenario analysis has been conducted in which TTD is assumed equal to PFS for selpercatinib.

		treatment for a short time upon disease progression.[1] For BSC, TTD is not considered in the economic model due to no costs being associated with treatment.	
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.	No scenario analyses have been conducted varying this assumption as it aligns with UK clinical practice.
	In the 4th treatment cycles and beyond, to account for dose reductions for selpercatinib, a proportion of patients were assumed to receive a reduced dose to match the relative dose intensities for selpercatinib observed in LIBRETTO-001, as outlined in Section B.3.5.1.	This is aligned with the available data from the LIBRETTO-001 and the SmPC for selpercatinib.	No scenario analyses have been conducted varying this assumption as it aligns with available data from LIBRETTO-001 and the SmPC for selpercatinib.
Subsequent treatments	Patients in both treatment arms are assumed to receive no active subsequent treatments.	As described in Section B.3.5.2, following disease progression, patients receiving selpercatinib or BSC are assumed to receive no active subsequent treatments. This is because no subsequent treatments are available following treatment with second-line selpercatinib or BSC. This approach is aligned with that used in TA742 and support by feedback from UK clinical experts.[3]	No scenario analyses have been conducted varying this assumption as it aligns with anticipated UK clinical 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*	No scenario analyses have been conducted varying this assumption as it represents a conservative assumption and aligns with the Committee's preference in TA911 and TA742.

		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.	
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.[96]	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 any-line MTC and TC populations (Section B.3.4.2), and were associated with uncertainty due to small patient numbers. 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 used in the base case. This approach is aligned with that adopted in TA742.[3] These utility values were also accepted by the NICE Committee in TA516 and TA535, and preferred by the	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.[3]

		Committee in TA928 in the absence of robust and clinically plausible utilities derived from the relevant clinical trial.	
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.[26, 27]	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 are 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

Pairwise comparisons for selpercatinib versus BSC have been conducted for the base case. A summary of the probabilistic base case pairwise comparisons for selpercatinib (at PAS price) versus BSC in *RET*-mutant MTC are presented in Table 89, with net health benefit (NHB) results presented in Table 90 (at selpercatinib PAS price).

The probabilistic base case cost-effectiveness results (at selpercatinib PAS price) show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be £[redacted] compared with £17,080 for patients treated with BSC (an incremental cost of £[redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with 1.51 for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of £47,795 per QALY gained versus BSC, respectively. At a willingness-to-pay threshold (WTP) of £30,000, 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 BSC.

The results presented include the confidential PAS discount provided alongside this submission.

Table 89: Pairwise probabilistic base-case results for selpercatinib versus BSC in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	17,080	2.67	1.51	[redacted]	[redacted]	[redacted]	47,795

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

Table 90: Probabilistic net health benefit for selpercatinib versus BSC in *RET*-mutant MTC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Selpercatinib	[redacted]	[redacted]	-	-	-	-
BSC	17,080	1.51	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; 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 91 (at selpercatinib PAS price), with NHB results presented in Table 92.

The probabilistic base case cost-effectiveness results (at selpercatinib PAS price) show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be £[redacted] compared with £16,059 for patients treated with BSC (incremental costs are £[redacted]). The total QALYs for patients receiving selpercatinib and BSC are estimated to be [redacted] and 1.27, respectively (an incremental QALY gain of [redacted]). This results in an ICER for selpercatinib versus BSC of £45,120 per QALY gained. The NHB at a £30,000 WTP is negative for BSC ([redacted]). 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.

Table 91: Pairwise probabilistic base-case results for selpercatinib versus 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)
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	16,059	2.31	1.27	[redacted]	[redacted]	[redacted]	45,120

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

Table 92: Probabilistic net health benefit for selpercatinib versus BSC for *RET* fusion-positive TC (at selpercatinib PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Selpercatinib	[redacted]	[redacted]	-	-	-	-
BSC	16,059	1.27	[redacted]	[redacted]	[redacted]	[redacted]

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

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 BSC are presented in Figure 41 and Figure 42.

Figure 41: Cost-effectiveness plane scatterplot for selpercatinib versus 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 42: Cost-effectiveness acceptability curves for selpercatinib versus 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 BSC are presented in Figure 43 and Figure 44.

Figure 43: Cost-effectiveness plane scatterplot for selpercatinib versus 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 44: Cost-effectiveness plane scatterplot for selpercatinib versus 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 DSA for the analysis of selpercatinib versus BSC are presented as a tornado plot in Figure 45. The most influential parameters were the discount rate (outcomes and costs), the progression-free health state utility value and the progression-free health state costs.

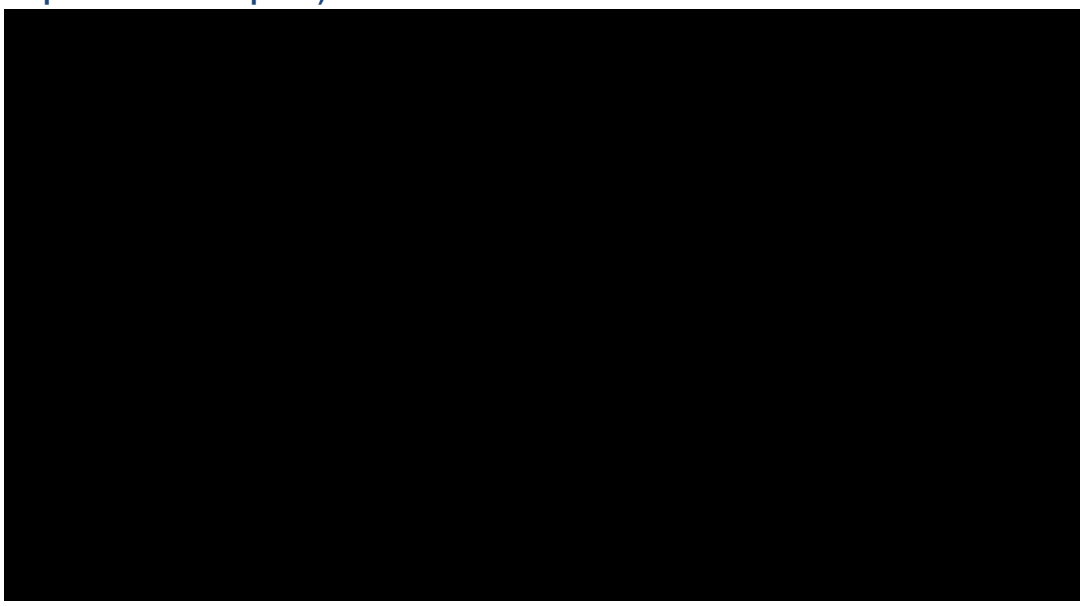
Figure 45: Tornado plot (ICER) of selpercatinib versus BSC – *RET*-mutant MTC (at selpercatinib PAS price)

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

RET fusion-positive TC

The 25 most influential variables in the DSA for the analysis of selpercatinib versus BSC are presented as a tornado plot in Figure 46. The most influential parameters were the discount rate (outcomes and costs), the progression-free health state utility value and the progression-free health state costs.

Figure 46: 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 and *RET* fusion-positive TC are presented in Table 93 (at selpercatinib PAS price).

Table 93: Scenario analyses (probabilistic) for the *RET*-mutant MTC and *RET* fusion-positive TC populations (at selpercatinib PAS price)

Scenario	Base case	Scenario analysis	Incremental costs	Incremental QALYs	ICER (£/QALY)
***RET*-mutant MTC population**					
Selpercatinib versus BSC: base case			[redacted]	[redacted]	**47,795**
PFS extrapolation (both treatment arms)	Loglogistic	Gamma	[redacted]	[redacted]	45,542
		Spline knot 1	[redacted]	[redacted]	48,436
OS extrapolation (both treatment arms)	Stratified Weibull (2.0 adjustment factor applied to selpercatinib)	Stratified gamma (2.0 adjustment factor applied to selpercatinib)	[redacted]	[redacted]	40,159
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	46,508
***RET* fusion-positive TC population**					
Selpercatinib versus BSC: base case			[redacted]	[redacted]	**45,120**
PFS extrapolation (both treatment arms)	Stratified Weibull	Exponential	[redacted]	[redacted]	46,803
OS extrapolation (both treatment arms)	Piecewise exponential (1.2 adjustment factor applied to selpercatinib)	Weibull (1.2 adjustment factor applied to selpercatinib)	[redacted]	[redacted]	41,385
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted] weeks	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	43,305

As outlined in Section B.3.6, selpercatinib is eligible for a 1.2x severity modifier versus BSC in the MTC and TC populations. This severity modifier is not included in the above cost-effectiveness results.

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; MTC: medullary thyroid cancer; PFS: progression free survival; QALYs: quality-adjusted life years; RET: rearranged during transfection; TC: thyroid cancer; TTD: time to discontinuation.

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 costs and outcomes) and the progression-free health state utility value and costs – with all scenarios 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 ~£2,000 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 'people aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib' and 'people aged 12 years and older who with advanced *RET*-mutant MTC require systemic therapy after cabozantinib or vandetanib' 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 BSC 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 routinely available to patients with advanced *RET* fusion-positive TC and advanced *RET*-mutant MTC who require systematic therapy following prior treatments with MKIs in the UK. Currently, patients whose disease has progressed on first-line therapy can receive selpercatinib via the CDF, but without access to selpercatinib via routine commissioning, the only alternative option for previously treated patients is palliative treatment with BSC. BSC is not an active treatment, and as such, it is associated with a poor prognosis.

With highly specific and potent targeting of *RET* alterations, selpercatinib represents an effective alternative treatment option to BSC. Selpercatinib offers a tolerable AE profile for an active treatment for patients with *RET*-altered thyroid cancer who do not respond to or have progressed on prior systemic therapy. As such, a positive recommendation for selpercatinib would represent a substantial benefit for patients with advanced *RET*-fusion positive TC and *RET*-mutant MTC who would otherwise face an extremely poor prognosis, by providing a routinely available, effective active treatment option.

In addition, there are currently no active treatment options for adolescent patients aged 12–17 years old with *RET*-altered MTC and TC who require systemic therapy following prior systemic treatment, so these patients typically receive BSC, with some clinicians requesting active treatment (i.e., MKIs) through compassionate use.[69] Therefore, selpercatinib would represent the first routinely available active treatment in the second-line setting for this patient population. The availability of a novel treatment for those who can presently have no active treatment options in this setting may offer hope to patients and their families of delayed disease progression and

improved survival. This benefit is not captured in the QALY calculations. Furthermore, 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,[97] 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, TA535, TA742 and ID6132).[3, 26, 27, 67]

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.[3] 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 BSC in this appraisal. As the model is largely consistent with the model used in 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 the ongoing selpercatinib appraisal in untreated advanced thyroid cancer with *RET* alterations (ID6132).[3, 69]

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 previously received systemic treatment, cross validation was not possible.

Clinical expert opinion

As part of TA742 and NICE ID6132, input from clinical experts 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.

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 after cabozantinib or vandetanib was evaluated versus BSC. For patients with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib, the cost-effectiveness of selpercatinib was evaluated versus BSC.

For *RET*-mutant MTC, the results of the pairwise probabilistic cost-effectiveness analysis demonstrate that the total costs associated with selpercatinib (at PAS price) and BSC are £[redacted] and £17,080, respectively. The total QALYs associated with selpercatinib and BSC are [redacted] and 1.51, respectively. The resulting pairwise ICER is £47,795 per QALY for selpercatinib versus BSC. As noted in Section B.3.6, selpercatinib is eligible for a 1.2x severity modifier versus BSC but this severity modifier is not included in these cost-effectiveness results.

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) and BSC are £[redacted] and £16,059, respectively. The total QALYs associated with selpercatinib and BSC are [redacted] and 1.27, respectively. The resulting ICER for selpercatinib versus BSC is £45,120. As noted in Section B.3.6, selpercatinib is eligible for a 1.2x severity modifier versus BSC but this severity modifier is not included in these cost-effectiveness results.

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 (costs and outcomes) and the progression-free health state utility value and costs; while the ICER increased by a maximum of ~£2,000 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.[3, 27]

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, providing data with greater median follow-up than available for the original submission in this indication, TA742. 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 BSC. As such, relative 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. The use of the any-line populations for MTC and TC will slightly overestimate OS and PFS for selpercatinib, compared with the prior systemic therapy population for MTC and TC, which represent the populations of interest for this submission. However, this was required due to the absence of published data for endpoints of interest for a prior systemic therapy population from EXAM or SELECT to inform the efficacy of BSC. As such, any-line populations were also used to inform the efficacy of the comparators, so this is not expected to be a significant source of bias in the ITCs.

Overall, 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 BSC, 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 previously received systemic therapy), selpercatinib provides a targeted treatment option that drives deep and durable responses, with substantially improved PFS and OS. Moreover, selpercatinib provides a tolerable active treatment option that would be available to a broad 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 BSC in UK clinical practice, and provide patients who otherwise face a poor prognosis with an effective alternative treatment option. Considering the severity of the disease, selpercatinib represents a cost-effective use of NHS resources when compared with BSC for patients with advanced, *RET*-altered thyroid cancer.

Compared with the original appraisal for selpercatinib in patients with *RET*-altered, advanced thyroid cancer following prior systemic therapy (TA742), data from LIBRETTO-001 are available with approximately two years of additional median follow-up. Furthermore, since the 16th December 2019 DCO informing TA742, the number of patients included has increased substantially in both the prior systemic therapy TC and prior cabozantinib/vandetanib MTC analysis sets. This is particularly meaningful for the prior systemic therapy RET fusion-positive TC population, for which the number of patients increased from 19 to 41 between the DCOs. Furthermore, [redacted]. This substantially reduces the uncertainty associated with the clinical and cost-effectiveness estimates for selpercatinib in the indications of interest and provides compelling evidence for selpercatinib to become available via routine commissioning in UK clinical practice.

References

1. Medicines and Healthcare products Regulatory Agency. Summary of Products Characteristics. Retsevmo 40 mg hard capsule. Available from: https://mhraproducts4853.blob.core.windows.net/docs/860f80184d66809a5920fbe65478fff1d25f3542. [Last accessed: 12th May 2023].
2. European Medicines Agency. Retsevmo. EPAR Product Information. Available from: https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_en.pdf. [Last Accessed: 20th March 2024].
3. National Institute for Health and Care Excellence. TA742: Selpercatinib for treating advanced thyroid cancer with RET alterations. Available from: https://www.nice.org.uk/guidance/ta742. [Last accessed: 25th April 2023].
4. National Institute for Health and Care Excellence. TA911: Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta911. [Last accessed: 24th October 2023].
5. European Medicines Agency. Retsevmo. Selpercatinib. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo. [Last Accessed: 19th June 2023].
6. National Institute for Health and Care Excellence. TA760: Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta760. [Last accessed: 26th April 2023].
7. Wadsley J, Beasley M, Garcez K, et al. Guidelines on the Use of Systemic Therapy in Patients with Advanced Thyroid Cancer. Clinical Oncology 2023;35:57–64.
8. National Health Service. National genomic test directory. Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/. [Last accessed: 26th April 2023].
9. National Health Service England. Accelerating genomic medicine in the NHS. Available from: https://www.england.nhs.uk/long-read/accelerating-genomic-medicine-in-the-nhs/. [Last accessed: 28th April 2023].
10. Drilon AE, Subbiah V, Oxnard GR, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. Journal of Clinical Oncology 2018;36.
11. Mulligan LM. 65 YEARS OF THE DOUBLE HELIX: Exploiting insights on the RET receptor for personalized cancer medicine. Endocrine-Related Cancer 2018;25:T189-T200.
12. Cancer Research UK. Thyroid cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer [Last accessed: 25th April 2023].
13. Cancer Research UK. Types of thyroid cancer. Available at: https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/stages-types/types. [Last accessed: 25th April 2023].
14. Roy M, Chen H, Sippel RS. Current understanding and management of medullary thyroid cancer. The Oncologist 2013;18:1093.
15. Agrawal N, Akbani R, Aksoy BA, et al. Integrated Genomic Characterization of Papillary Thyroid Carcinoma. Cell 2014;159:676-690.
16. Drilon A, Hu ZI, Lai GGY, et al. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nature Reviews Clinical Oncology 2018;15:151-167.
17. Santoro M, Carlomagno F. Central role of RET in thyroid cancer. Cold Spring Harbor perspectives in biology 2013;5:a009233.

18. Cancer Research UK. Thyroid Cancer. Available from: https://www.cancerresearchuk.org/cancer-type/thyroid-cancer. [Last accessed: 28th April 2023].
19. American Cancer Society. Thyroid Cancer Survival Rates, by Type and Stage. Available from: https://www.cancer.org/cancer/types/thyroid-cancer/detection-diagnosis-staging/survival-rates.html. [Last accessed: 25th April 2023].
20. Gou J, Cheng W, Lei J, et al. Health-related quality-of-life assessment in surgical patients with papillary thyroid carcinoma: A single-center analysis from Mainland China. Medicine 2017;96.
21. Helvacı BC, Yalçın MM, Şehnaz SNG, et al. Differentiated thyroid cancer: effect on quality of life, depression, and anxiety. Hormones. 2023;22:367-374.
22. Singer S, Husson O, Tomaszewska IM, et al. Quality-of-life priorities in patients with thyroid cancer: a multinational european organisation for research and treatment of cancer phase I study. Thyroid 2016;26:1605-1613.
23. Hadoux J, Schlumberger M. Chemotherapy and tyrosine-kinase inhibitors for medullary thyroid cancer. Best Practice & Research Clinical Endocrinology & Metabolism 2017;31:335-347.
24. Wells Jr SA, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the American Thyroid Association Guidelines Task Force on medullary thyroid carcinoma. Thyroid 2015;25:567-610.
25. Tappenden P, Carroll C, Hamilton J, et al. Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model. Health Technology Assessment 2019;23:1-144.
26. National Institute for Health and Care Excellence. TA516: Cabozantinib for treating medullary thyroid cancer. Available at: https://www.nice.org.uk/guidance/ta516 [Last accessed: 25th April 2023].
27. National Institute for Health and Care Excellence. TA535: Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta535 [Last accessed: 25th April 2023].
28. Mitchell AL, Gandhi A, Scott-Coombes D, et al. Management of thyroid cancer: United Kingdom national multidisciplinary guidelines. The Journal of Laryngology & Otology 2016;130:S150-S160.
29. Cancer Research UK. What is thyroid cancer? Available from: https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/about-thyroid-cancer [Last accessed: 26th June 2020].
30. Endocrineweb. Thyroid Gland: Overview. Available from: https://www.endocrineweb.com/conditions/thyroid-nodules/thyroid-gland-controls-bodys-metabolism-how-it-works-symptoms-hyperthyroi [Last accessed: 26th June 2020].
31. Cancer.net. Thyroid Cancer. Available at: https://www.cancer.net/cancer-types/thyroid-cancer. [Last accessed: 25th April 2023].
32. Carlomagno F. Thyroid cancer: role of RET and beyond. European Thyroid Journal 2012;1:15-23.
33. El Osta B, Ramalingam SS. RET Fusion: Joining the Ranks of Targetable Molecular Drivers in NSCLC. JTO Clinical and Research Reports 2020;1:1-11.
34. Prescott JD, Zeiger MA. The RET oncogene in papillary thyroid carcinoma. Cancer 2015;121:2137-2146.
35. Santoro M, Moccia M, Federico G, et al. RET Gene Fusions in Malignancies of the Thyroid and Other Tissues. Genes 2020;11:424.
36. Kohno T, Tabata J, Nakaoku T. REToma: a cancer subtype with a shared driver oncogene. Carcinogenesis 2020;41:123-129.

37. Landa I, Ibrahimpasic T, Boucai L, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. The Journal of clinical investigation 2016;126:1052-1066.
38. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. Clinical endocrinology 2014;81:1-122.
39. Nikiforov YE, Rowland JM, Bove KE, et al. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. Cancer Research 1997;57:1690-1694.
40. Thomas GA, Bunnell H, Cook HA, et al. High prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas: a strong correlation between RET/PTC3 and the solid-follicular variant. The Journal of Clinical Endocrinology & Metabolism 1999;84:4232-4238.
41. Nikiforov YE, Erickson LA, Nikiforova MN, et al. Solid variant of papillary thyroid carcinoma: incidence, clinical–pathologic characteristics, molecular analysis, and biologic behavior. The American journal of surgical pathology 2001;25:1478-1484.
42. Eli Lilly Data on File. Thyroid Cancer Clinical Expert Validation Interviews. Meeting Minutes. 2020.
43. The World Health Organisation. International Agency for Research on Cancer. Cancer Today. Available from: https://gco.iarc.fr/. [Last accessed: 11th May 2023].
44. Pizzato M, Li M, Vignat J, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. The Lancet Diabetes & Endocrinology 2022;10:264-72.
45. IARC. Lung cancer fact sheet. Source: GLOBOCAN 2018. International Agency for Research on Cancer. Volume 2020: World Health Organization, 2018.
46. National Cancer Registration and Analysis Service. Thyroid cancer – trends by sex, age and histological type. Available from: http://ncin.org.uk/publications/data_briefings/thyroid_cancer_trends_by_sex_age_and_histological_type#. [Last accessed: 22nd June 2023]. .
47. Bai Y, Kakudo K, Kwon Jung C. Updates in the Pathologic Classification of Thyroid Neoplasms: A Review of the World Health Organization Classification. Endocrineology and Metabolism 2020;35:696-715.
48. Cancer Research UK. Thyroid cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer/incidence. [Last accessed: 28th April 2023].
49. Cancer Research UK. Survival for thyroid cancer. Available from: https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/survival. [Last accessed: 26th April 2023].
50. Simões-Pereira J, Macedo D, Bugalho MJ. Clinical outcomes of a cohort of patients with central nervous system metastases from thyroid cancer. Endocrine connections 2016;5:82.
51. Gomes-Lima CJ, Wu D, Rao SN, et al. Brain Metastases From Differentiated Thyroid Carcinoma: Prevalence, Current Therapies, and Outcomes. Journal of the Endocrine Society 2019;3:359-371.
52. Ullmann TM, Thiesmeyer JW, Lee YJ, et al. RET Fusion-Positive Papillary Thyroid Cancers are Associated with a More Aggressive Phenotype. Annals of Surgical Oncology 2022;29:4266-4273.
53. Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. The Journal of Clinical Endocrinology & Metabolism 2008;93:682-687.
54. Schlumberger M, Elisei R, Müller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Annals of Oncology 2017;28:2813-2819.

55. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. New England Journal of Medicine 2015;372:621-630.
56. Thyroid Cancer Center. Diagnosis of Papillary Thyroid Cancer. Available at: https://www.thyroidcancer.com/thyroid-cancer/papillary/diagnosis [Last accessed: 26th June 2020].
57. Hirst C, Kern DM, Zhou S, et al. Resource Use Associated with Patients with Thyroid Cancer in a United States Insured Population. Value in Health 2014;17:A96.
58. Endocrine Society. Facts and figures: thyroid cancer. 1st ed. 2017. Available at: https://www.endocrine.org/-/media/endocrine/files/facts-and-figures/endocrine_facts_figures_cancers_and_neoplasias.pdf [Last accessed: 4th September 2020].
59. Mengmeng L, Meheus F, Polazzi S, et al. The Economic Cost of Thyroid Cancer in France and the Corresponding Share Associated With Treatment of Overdiagnosed Cases. Value in Health 2023;26:1175-1182.
60. Ramsey S, Blough D, Kirchhoff A, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health affairs 2013;32:1143-1152.
61. Uppal NBS, Cunningham C, James B. The Cost and Financial Burden of Thyroid Cancer on Patients in the US: A Review and Directions for Future Research. JAMA Otolaryngology– Head & Neck Surgery 2022;148:568–575.
62. Ratzon NZ, Uziely B, de Boer AGEM, et al. Unemployment risk and decreased income two and four years after thyroid cancer diagnosis: a population-based study. Thyroid 2016;26:1251-1258.
63. Papaleontiou M. Financial Toxicity Is Associated with Poorer Quality of Life in Thyroid Cancer Survivors. Clinical Thyroidology 2020;32:83–85.
64. National Institute for Health and Care Excellence. NG230: Thyroid cancer: assessment and management. Available from: https://www.nice.org.uk/guidance/ng230/resources/thyroid-cancer-assessment-and-management-pdf-66143889414853. [Last accessed: 25th April 2023].
65. National Institute for Health and Care Excellence. TA550: Vandetanib for treating medullary thyroid cancer. Available at: https://www.nice.org.uk/guidance/ta550 [Last accessed: 25th April 2023].
66. National Institute for Health and Care Excellence. TA928: Cabozantinib for previously treated advanced differentiated thyroid cancer unsuitable for or refractory to radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta928 [Last accessed: 16th January 2024].
67. National Institute for Health and Care Excellence. ID6132: Selpercatinib for untreated advanced thyroid cancer with RET alterations. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11047. [Last accessed: 14th February 2024].
68. Lu Z, Zhang Y, Feng D, et al. Targeted next generation sequencing identifies somatic mutations and gene fusions in papillary thyroid carcinoma. Oncotarget 2017;8:45784.
69. Eli Lilly Data on File. Selpercatinib for untreated advanced RET altered TC and MTC Clinical Expert Validation Interviews. Meeting Minutes. 2023.
70. Fleeman N, Houten R, Chaplin M, et al. A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. BMC cancer 2019;19:1209.
71. NHS England. National Cancer Drugs Fund List. 19th October 2023. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/NationalCDF_List_ver1.278_-19102023_MASTER.pdf. [Last accessed: 20th October 2023].
72. Vodopivec DM, Hu MI. RET kinase inhibitors for RET-altered thyroid cancers. Ther Adv Med Oncol 2022;14:17588359221101691.

73. 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.
74. Wirth LJ, Brose MS, Subbiah V, et al. Durability of Response With Selpercatinib in Patients With RET-Activated Thyroid Cancer: Long-Term Safety and Efficacy From LIBRETTO-001. Journal of Clinical Oncology 2024:JCO. 23.02503.
75. NHS England. Systemic Anti-Cancer Therapy Dataset: Selpercatinib for treating advanced thyroid cancer with RET alterations – data review.
76. Phillippo DM AA, Dias S, Palmer S, Abrams KR, Welton NJ,. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016. Available at: http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf [Last accessed: 15th September 2020].
77. ClinicalTrials.gov. NCT03157128. A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). Available from: https://clinicaltrials.gov/ct2/show/NCT031571.
78. Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).
79. Eli Lilly Data on File. LIBRETTO-001 SAP Version 3 (19th December 2022 Approval).
80. Raez LE, Kang H, Ohe Y, et al. Patient Reported Outcomes with Selpercatinib in Patients with RET driven cancers in the Phase 1/2 LIBRETTO-001 Trial. ESMO 2023:FPN 669P.
81. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
82. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.
83. Wirth LJ, Cabanillas ME, Sherman EJ, et al. Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET-altered thyroid cancers: an update from ASCO 2018, 2018.
84. Oxnard GR, Subbiah V, Park K, et al. Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET fusion+ non-small cell lung cancer: An update from ASCO 2018, 2018.
85. Wirth L, Sherman E, Drilon A, et al. Registrational results of LOXO-292 in patients with RET-altered thyroid cancers. Annals of Oncology 2019;30:v933.
86. European Organisation for Research and Treatment of Cancer. FAQ. Available from: https://qol.eortc.org/faq-category/scoring/. [Last accessed: 29th August 2023].
87. Musoro JZ, Coens C, Fiteni F, et al. Minimally Important Differences for Interpreting EORTC QLQ-C30 Scores in Patients With Advanced Breast Cancer. JNCI Cancer Spectrum 2019;3:pkz037.
88. Signorovitch JE, Wu EQ, Andrew PY, et al. Comparative effectiveness without head-to-head trials. Pharmacoeconomics 2010;28:935-945.
89. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value in Health 2012;15:940-947.
90. Wells Jr SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. Journal of clinical oncology 2012;30:134.
91. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. Journal of clinical oncology 2013;31:3639.
92. Sherman SI, Clary DO, Elisei R, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer 2016;122:3856-3864.
93. 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.
94. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384:319-328.
95. Hu MI, Elisei R, Dedecjus M, et al. Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer. Endocr Relat Cancer 2019;26:241-250.
96. 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.
97. NICE. Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed: 19/08/20].
98. Central Statistics Office. CPM01: consumer price index by commodity group (health), month and statistic (Base Dec 2016=100, all months). 2023. Available at: https://www.ons.gov.uk/economy/inflationandpriceindices. [Last accessed: 23rd October 2023].
99. Guyot P, Ades A, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology 2012;12:9.
100. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. [Last Accessed: 20 September 2020].
101. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Statistics in medicine 2002;21:2175-2197.
102. 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.
103. Kontodimopoulos N, Aletras VH, Paliouras D, et al. Mapping the cancer-specific EORTC QLQ-C30 to the preference-based EQ-5D, SF-6D, and 15D instruments. Value Health 2009;12:1151-7.
104. Marriott ER, van Hazel G, Gibbs P, et al. Mapping EORTC-QLQ-C30 to EQ-5D-3L in patients with colorectal cancer. J Med Econ 2017;20:193-199.
105. National Institute for Health and Care Excellence. TA621: Osimertinib for untreated EGFR mutation–positive non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta621 [Last accessed: 13th October 2023].
106. Beusterien K, Szabo S, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. British journal of cancer 2009;101:387-389.
107. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health 2010;13:509-518.
108. British National Formulary. Selpercatinib. Medicinal Forms. Available from: https://bnf.nice.org.uk/drugs/selpercatinib-specialist-drug/#medicinal-forms. [Last accessed: 12th June 2023].
109. Curtis L, Burns A. Unit costs of health and social care: Personal Social Services Research Unit 2021, University of Kent, Canterbury. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/ [Last accessed: 23rd October 2023]. 2022.

110. Taccaliti A, Silvetti F, Palmonella G, et al. Genetic alterations in medullary thyroid cancer: diagnostic and prognostic markers. Curr Genomics 2011;12:618-25.
111. Liu S, Gao A, Zhang B, et al. Assessment of molecular testing in fine-needle aspiration biopsy samples: An experience in a Chinese population. Experimental and Molecular Pathology 2014;97:292-297.
112. QALY Shortfall Calculator. Available at: https://r4scharr.shinyapps.io/shortfall/. [Accessed: 19/08/2022].
113. National Institute for Health and Care Excellence. NICE health technology evaluations Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technologyevaluation. Accessed: 08/07/2022.
114. Mapping-5L-to-3L-DSU-report.pdf. Hernandez-Alava M, Wailoo A, Pudney S. 2017. Available at: https://www.sheffield.ac.uk/media/34125/download?attachment [Last accessed: 17th October 2023].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
ID6288_Selpercatinib in TC_SIP_Final_12Apr24	Final	Yes	12th April 2024

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

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 who have previously received the cancer treatments lenvatinib or sorafenib
- Patients 12 years and older with **advanced, *RET*-mutant medullary thyroid cancer** (MTC), who require cancer treatment and who have previously received the cancer treatments cabozantinib or vandetanib

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 advanced *RET*-mutant MTC in patients aged 12 years or older who have previously **received systemic cancer therapy** was granted by the **Medicines and Healthcare products Regulatory Agency** (MHRA) in March 2021. This marketing authorisation was then expanded to include patients with advanced *RET*-mutant MTC had not

previously received the cancer treatments cabozantinib or vandetanib. This marketing authorisation was granted in February 2023.

Marketing authorisation for selpercatinib for the treatment of advanced *RET*-fusion positive TC in adults who have previously received systemic cancer therapy was granted in March 2021. This marketing authorisation is being expanded to cover people aged 12 years and older with advanced *RET*-fusion positive TC who have not previously received a systemic cancer therapy. This marketing authorisation from the MHRA has not been received yet.

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

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 in people aged 12 years and older who require cancer treatment and who have previously received systemic treatment for their cancer (sorafenib or lenvatinib)
- Advanced *RET*-mutant MTC in people aged 12 years and older who require cancer treatment and who have previously received systemic treatment for their cancer (cabozantinib or vandetanib)

What are 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 develops 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

There is currently limited evidence available investigating how changes in the *RET* gene impact the survival of patients with TC. However, changes in *RET* do not seem to have an overall effect on the life expectancy of patients with TC.[10-13] For patients with MTC, however, changes in *RET* can 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 a 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.[14]

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.[15]

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). MKIs are systemic therapies that work by blocking proteins called kinases. This stops the cancer from growing and spreading. They are often taken as tablets.

As lenvatinib and sorafenib are only available for adult patients (people 18 years old and older), patients with advanced TC who are aged between 12 to 17 years old are only able to receive **best supportive care (BSC)**. BSC is when a patient is given medicines to reduce pain and make them as comfortable as possible. BSC does not treat the cancer. Some patients aged between 12 to 17 years old may be able to receive MKIs through **compassionate use**.

If a patient with DTC needs further treatment after receiving their first systemic cancer therapy, selpercatinib is an option for patients with advanced *RET*-altered TC. Selpercatinib is currently available for these patients through the **Cancer Drugs Fund (CDF).** The CDF temporarily funds new cancer therapies, while more data are collected on the safety and effectiveness of the drug. The only other treatment option is BSC. If selpercatinib stops being funded, patients will then only be able to receive BSC.

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.

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.[16] Chemotherapies are sometimes given by an intravenous drip or injection into the blood, which requires patients to receive these treatments in hospital.[17]

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.[14]

Selpercatinib is available through the CDF for patients with *RET*-altered ATC as a **first-line treatment**. For more information on selpercatinib see **Section 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.[14]

Cabozantinib is another MKI, which is a type of systemic therapy. In the UK, cabozantinib is the only first-line 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.[18]

Cabozantinib can only be given to adult patients (people over 18 years old). This means that for patients with advanced MTC who are aged between 12 to 17 years old, BSC is the only treatment option. However, some patients aged between 12 to 17 years old may be able to access cabozantinib through compassionate use.

If a patient with MTC needs further cancer treatment after receiving cabozantinib, selpercatinib is available through the CDF. The only other treatment option available is BSC. Therefore, if selpercatinib stops being funded, the only treatment available to these patients will be BSC.

Comparators to selpercatinib

For patients with *RET*-altered TC and MTC, the comparator to selpercatinib is BSC.

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 **health-related quality of life** (HRQoL) measures in the selpercatinib trial. The outcomes of the HRQoL measures from the key trial (LIBRETTO-001) are presented in **Section 3f.** 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.[19, 20]

Studies have shown that patients with PTC have a poorer HRQoL than the general population.[19] 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.[21] Patients can also suffer from increase anxiety and depression.[22]

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 severe impact on these patients quality of life and mental health.[23]

Currently, there is not much information on how *RET* fusion-positive TC and *RET*-mutant MTC impact patients' HRQoL, especially for patients with *RET*-altered TC and MTC who have progressed on prior cancer treatment. This is because most studies look at TC and MTC, with very few focussing only on *RET* fusion-positive TC and *RET*-mutant MTC. However, patients with advanced *RET*-fusion positive TC and *RET*-mutant MTC have a lack of treatment options. Currently, only selpercatinib and BSC are available. BSC does not treat the cancer, and selpercatinib is temporarily available through the CDF. This lack of treatment options may have a negative impact on patients' mental health and wellbeing.[23]

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.[21] 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.[24]

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

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 kinase. By doing this it can stop the growth and spread TC and MTC that have altered RET proteins.

Selpercatinib is a type of **targeted therapy** that works by blocking RET receptor tyrosine kinases. This means that selpercatinib is a well-tolerated active cancer treatment. For more information on the safety of selpercatinib see **Section 3g**.

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.

No – 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 hard capsule. 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.[25]

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 or three tablets), twice a day.
- Patients weighing 50 kg or more will take two capsules 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.[25]

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.

LIBRETTO-001 (Clinical trial number: NCT03157128)[26, 27]

LIBRETTO-001 is the clinical trial that provides evidence on the efficacy and safety of selpercatinib as a treatment for patients with *RET* fusion-positive TC and *RET*-mutant MTC who have previously received a systemic cancer treatment.

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 be enrolled in the part of the trial studying thyroid cancer, patients had to be 12 years or older and have advanced TC with *RET* fusions or advanced MTC with *RET* mutations. In total, 152 patients with MTC with *RET* mutations (who had previously received cabozantinib or vandetanib) and 41 patients with TC with *RET* fusions (who had received a 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. More information on the trial design and methods can be found in **Document B** in **Section B.2.2** and **Section B.2.3**.

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

The LIBRETTO-001 clinical trial studied selpercatinib for the treatment of patients with TC and MTC who have previously received systemic cancer therapy. It is a Phase I/II trial, which 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 have previously received cabozantinib or vandetanib or patients with *RET* fusion-positive TC who have previously received a 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 78% for patients with *RET*-mutant MTC and 85% for patients with *RET* fusion-positive TC.[28]

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 66% 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 51% of patients.[28]

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, 65% 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, 57% of patients survived without their disease getting any worse for at least two years after their treatment started.[28]

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 particularly small. This is a limitation of the study, as it means there is some uncertainty about the efficacy and safety of selpercatinib. However, data on a greater number of patients are now available, compared with when NICE originally appraised selpercatinib in these populations (TA742).

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.

Systemic Anti-Cancer Therapy dataset

Results for the effectiveness of selpercatinib in UK clinical practice are also available through the Systemic Anti-Cancer Therapy (SACT) dataset. This dataset collects information about patients who are receiving selpercatinib in the UK outside of clinical trials. However, this dataset only includes a very small number of patients, only includes patients with MTC, and has collected information on these patients for a shorter time than the LIBRETTO-001 trial.

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.

As such, it was necessary to perform indirect treatment comparisons for selpercatinib versus BSC for patients with TC and MTC. 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 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 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-C30): 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-C30 data were collected for patients with MTC and TC. These patients either had or had not previously received a systemic cancer treatment. 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.[29]

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.

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:[28]

- 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):[30]

- 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:[28]

- 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:[28]

- Alanine aminotransferase (ALT) increase (the amount of a protein called ALT in your blood is higher than normal. This may mean that your liver is damaged)[31]
- Aspartate aminotransferase (AST) increase (the amount of a protein called AST in your blood is higher than normal. This may mean that your liver is damaged)[31]

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.

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 following prior systemic cancer treatment

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 64% of patients with *RET*-mutant MTC and 57% 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 BSC for patients with *RET* fusion-positive TC and *RET*-mutant MTC.

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.[19, 20, 24] For patients with MTC, diarrhoea can also impact their HRQoL. The LIBRETTO-001 trial showed that selpercatinib treatment led to improvements in the HRQoL of 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 BSC.

Selpercatinib provides an active treatment option for patients who would otherwise only receive BSC

In the UK, first-line treatments for patients with advanced *RET*-altered TC and MTC consist of MKIs. These include lenvatinib and sorafenib (for TC) and cabozantinib (for MTC). However, for some patients these treatments do not work and they experience disease progression.[15, 32]

For these patients, selpercatinib is currently available through the CDF as a second-line treatment. BSC is the only other treatment option for these patients in the UK.

This means that if selpercatinib stops being funded and is not made available in UK clinical practice, BSC will be the only option left for these patients. BSC provides pain relief and manages symptoms but does not treat the cancer. Therefore, there is a need for these patients to have continued access to selpercatinib, which can effectively treat advanced *RET*-altered TC and MTC. By making selpercatinib routinely available in the UK, this need can be addressed.

Selpercatinib provides a treatment option for patients aged 12–17 years

Currently, adolescent patients (people aged between 12 to 17 years old) with *RET*-altered TC and MTC can only receive BSC in the UK. This is because the MKIs cabozantinib, lenvatinib and sorafenib can only be given to adult patients.[18, 20] However, some patients are still able to receive them through compassionate use. For these patients, selpercatinib would be a readily available and effective treatment option following prior systemic therapy.

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 or reducing the dose of 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 which means that, for most patients, treatment with selpercatinib will be manageable. Therefore, the chance that a patent will need to stop treatment with selpercatinib due to unpleasant side effects is low. 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 treatment, called the comparator (BSC) for both patients with *RET* fusion-positive TC and 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 across oncology 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 either have treatment with selpercatinib or they receive BSC. 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 comparator, BSC, 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 (35 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 BSC, it is anticipated that patients receiving selpercatinib will remain progression-free for longer compared to BSC 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.[33] It is also anticipated that patients receiving selpercatinib will remain alive for a longer period of time compared to BSC 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. Selpercatinib is eligible for a severity modifier when compared with BSC in both the *RET* fusion-positive TC and *RET*-mutant MTC populations.

Overall, the results of the economic analysis showed selpercatinib to be associated with increased costs and increased QALYs when compared to BSC. For the *RET*-mutant MTC population, the ratio of costs and QALYs for selpercatinib compared with BSC was £47,795 per QALY. For the *RET* fusion-positive TC population, the ratio of costs and QALYs for selpercatinib compared with BSC was £45,120 per QALY. As stated above, selpercatinib is eligible for a severity modifier 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.

Benefits of selpercatinib not captured in the economic analysis

Selpercatinib offers a treatment option 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, currently available treatments for patients with advanced *RET*-altered TC and MTC who have not previously received a systemic cancer treatment are MKIs. These include lenvatinib and sorafenib (for TC) and cabozantinib (for MTC). These first-line treatments are associated with poor survival and serious side effects. Therefore, many patients with *RET*-altered TC and MTC will experience disease progression or will stop their cancer treatment due to unpleasant side effects. For these patients who require further cancer treatment, selpercatinib is currently available through the CDF. BSC is the only other treatment option for these patients. Therefore, if selpercatinib stops being funded, BSC would be the only treatment available. BSC does not treat the cancer. There is therefore a high unmet need for selpercatinib to become routinely available in the UK, to remain an effective option for patients with advanced *RET*-altered TC and MTC.

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 minimal side effects. This means that patients rarely have to stop taking selpercatinib due to side effects. 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 BSC. 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

Females are more likely to develop thyroid cancer than males (**Section 2a**). Therefore, making selpercatinib routinely available in the UK will help to reduce the health inequalities experienced by female people with advanced TC and MTC.

Before a patient can be given selpercatinib, the doctor will need to know if they have a mutation in their *RET* gene (**Section 2b**). In England, this is possible through NGS testing, completed at Genomic hubs. Therefore, the need for this testing is not an equality concern.

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 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.
Compassionate use	A treatment option that allows a patient with a serious condition to access a currently unlicenced medicine, outside of a clinical trial.
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.
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).
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.
First-line treatment	The treatment that a patient receives if they need more cancer treatment following surgery or radiotherapy (for MTC), or surgery and radioactive iodine treatment (for TC).
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.
Health-related quality of life	The effect that a disease has on a person's overall health and wellbeing.
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.
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.
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).
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.
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.
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.
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 therapy/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:

1. Endocrineweb. Thyroid Gland: Overview. Available at: https://www.endocrineweb.com/conditions/thyroid-nodules/thyroid-gland-controls-bodys-metabolism-how-it-works-symptoms-hyperthyroi [Last accessed: 26th June 2020].
2. Cancer Research UK. Types of thyroid cancer. Available at: https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/stages-types/types. [Last accessed: 25th April 2023].
3. Carlomagno F. Thyroid cancer: role of RET and beyond. European Thyroid Journal 2012;1:15-23.
4. Cancer Research UK. What is thyroid cancer? Available at: https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/about-thyroid-cancer [Last accessed: 26th June 2020].
5. Thyroid Cancer Center. Diagnosis of Papillary Thyroid Cancer. Available at: https://www.thyroidcancer.com/thyroid-cancer/papillary/diagnosis [Last accessed: 26th June 2020].
6. Hadoux J, Schlumberger M. Chemotherapy and tyrosine-kinase inhibitors for medullary thyroid cancer. Best Practice & Research Clinical Endocrinology & Metabolism 2017;31:335-347.
7. Cancer Research UK. Thyroid cancer statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer [Last accessed: 25th April 2023].
8. Cancer Research UK. Thyroid cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer/incidence. [Last accessed: 28th April 2023].
9. American Cancer Society. Thyroid Cancer Survival Rates, by Type and Stage. Available from: https://www.cancer.org/cancer/types/thyroid-cancer/detection-diagnosis-staging/survival-rates.html. [Last accessed: 25th April 2023].
10. Nikiforov YE, Rowland JM, Bove KE, et al. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. Cancer Research 1997;57:1690-1694.
11. Nikiforov YE, Erickson LA, Nikiforova MN, et al. Solid variant of papillary thyroid carcinoma: incidence, clinical–pathologic characteristics, molecular analysis, and biologic behavior. The American journal of surgical pathology 2001;25:1478-1484.
12. Thomas GA, Bunnell H, Cook HA, et al. High prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas: a strong correlation between RET/PTC3 and the solid-follicular variant. The Journal of Clinical Endocrinology & Metabolism 1999;84:4232-4238.
13. Eli Lilly Data on File. Thyroid Cancer Clinical Expert Validation Interviews. Meeting Minutes. 2020.
14. Mitchell AL, Gandhi A, Scott-Coombes D, et al. Management of thyroid cancer: United Kingdom national multidisciplinary guidelines. The Journal of Laryngology & Otology 2016;130:S150-S160.
15. Fleeman N, Houten R, Chaplin M, et al. A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. BMC cancer 2019;19:1209.
16. Cancer Research UK. About side effects of chemotherapy. Available at: https://www.cancerresearchuk.org/about-cancer/treatment/chemotherapy/side-effects/about [Last accessed: 7th August 2023].

17. Cancer Research UK. How you have chemotherapy. Available at: https://www.cancerresearchuk.org/about-cancer/treatment/chemotherapy/how-you-have [Last accessed: 7th August 2023].
18. National Institute for Health and Care Excellence. TA516: Cabozantinib for treating medullary thyroid cancer. Available at: https://www.nice.org.uk/guidance/ta516 [Last accessed: 25th April 2023].
19. Gou J, Cheng W, Lei J, et al. Health-related quality-of-life assessment in surgical patients with papillary thyroid carcinoma: A single-center analysis from Mainland China. Medicine 2017;96.
20. National Institute for Health and Care Excellence. TA535: Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta535 [Last accessed: 25th April 2023].
21. Singer S, Husson O, Tomaszewska IM, et al. Quality-of-life priorities in patients with thyroid cancer: a multinational european organisation for research and treatment of cancer phase I study. Thyroid 2016;26:1605-1613.
22. Helvacı BC, Yalçın MM, Şehnaz SNG, et al. Differentiated thyroid cancer: effect on quality of life, depression, and anxiety. Hormones 2023. https://doi.org/10.1007/s42000-023-00449-3.
23. National Institute for Health and Care Excellence. TA742: Selpercatinib for treating advanced thyroid cancer with RET alterations. Available from: https://www.nice.org.uk/guidance/ta742. [Last accessed: 25th April 2023].
24. Papaleontiou M. Financial Toxicity Is Associated with Poorer Quality of Life in Thyroid Cancer Survivors. Clinical Thyroidology 2020;32:83–85.
25. Medicines and Healthcare products Regulatory Agency. Summary of Products Characteristics. Retsevmo 40 mg hard capsule. Available from: https://mhraproducts4853.blob.core.windows.net/docs/860f80184d66809a5920fbe65478fff1d25f3542. [Last accessed: 12th May 2023].
26. ClinicalTrials.gov. NCT03157128. A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). Available from: https://clinicaltrials.gov/ct2/show/NCT031571.
27. Eli Lilly and Company. Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).
28. 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.
29. Raez LE, Kang H, Ohe Y, et al. Patient Reported Outcomes with Selpercatinib in Patients with RET driven cancers in the Phase 1/2 LIBRETTO-001 Trial. ESMO 2023:FPN 669P.
30. The DIPG / DMG Resource Network. About side effects in clinical trials. Available at: https://www.dipg.org/treatment/clinical-trials/side-effects/ [Last accessed: 7th August 2023].
31. British Liver Trust. Liver blood tests. Available at: https://britishlivertrust.org.uk/information-and-support/living-with-a-liver-condition/liver-blood-tests/ [Last accessed: 1st March 2024].
32. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. Journal of clinical oncology 2013;31:3639.
33. 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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID6288

Clarification questions

April 2024

File name	Version	Contains confidential information	Date
ID6288 Company Response to Clarification_24May2024 [CIC]	1.0	Yes	24th May 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 (Heading 1)

Literature searches (Heading 2)

A 1. **Priority question: The EAG noted a number of structural limitations in the clinical effectiveness searches, which they would ask to be taken into account during any new searches. Specifically, given the structure of the search strategies, presented in appendix D.1.1. of the CS, and in particular the inclusion of facets for specific interventions, they were designed to identify:**

a) Single arm studies of any intervention in *RET*-altered TC (including MTC, PTC, and DTC)

b) RCTs, conducted in patients with MTC, irrespective of *RET*-mutation status, which included selpercatinib, cabozantinib or vandetanib as an intervention

c) RCTs, conducted in patients with PTC or DCT, irrespective of RET mutation status, which included selpercatinib, sorafenib or lenvatinib as an intervention

The comparator specified in the NICE scope (for both *RET*-mutant MTC and *RET*-fusion positive TC) is BSC or palliative care and the CS uses ITCs, with data from the placebo arms of RCTs (as a proxy for BSC), to generate estimates of the comparative efficacy of selpercatinib. In order to ensure that all potential sources of comparator data have been considered, searches should be designed to identify any study with a placebo or BSC arm, which has been conducted in one of the specified populations. Please conduct new literature searches which are not limited by intervention (taking into account the errors and limitations outlined below (A.2.).

Lilly have not conducted new literature searches within the timeframe of the clarification questions, and maintain that the searches used in the clinical systematic literature review (SLR) informing this submission were sufficiently robust.

It is important to clarify that the current search strategies already included all studies including patients with rearranged during transfection (*RET)*-altered thyroid cancer, regardless of intervention, meaning that no studies in patients with *RET*-altered thyroid cancer for placebo/best supportive care (BSC) were missed.

Therefore, theoretically, the only studies for placebo/BSC that would not have been captured in the current searches are single-arm studies or randomised controlled trials (RCTs) including a placebo/BSC arm that did not explicitly include patients with *RET*-altered thyroid cancer. It is considered unlikely that any single-arm studies would have been conducted including patients receiving placebo/BSC, given the ethical concerns that would be associated with such a study.

Therefore, it is only necessary to consider if any RCTs including placebo/BSC arms have been excluded from the SLRs. The searches included a comprehensive range of potentially used treatments for thyroid cancer, including selpercatinib, pralsetinib, cabozantinib and vandetanib (for medullary thyroid cancer [MTC]) and selpercatinib, pralsetinib, lenvatinib and sorafenib (for thyroid cancer [TC]). Therefore, the only studies which might have been omitted would be RCTs for alternative treatments that additionally included a placebo arm. However, as the searches already included all treatments recommended by NICE for the treatment of either TC and MTC, as well as additional treatments, such as pralsetinib, then it is considered that the current search strategy is extremely unlikely to have omitted any evidence that would be more relevant than the SELECT and EXAM trials used to inform the efficacy of BSC in the MTC and TC populations, respectively, given the paucity of other treatment options for patients with thyroid cancer.

A 2. The searches described in Appendix D as update searches appeared both overly complicated and contained a number of errors:

a) For all update searches: Given the low number of hits retrieved, the EAG feels that a simpler and more appropriate approach would have been to search for terms for thyroid cancer as a whole combined with a facet for RET mutations. With a date limit this would have resulted in manageable number of results (for example, a test search based on this structure with a 2019-C

date limit retrieved 905 records from Embase). Please consider this advice in any new literature searches.

Lilly thank the EAG for this suggestion. As previously detailed in response to Q A.1, while it is acknowledged that the algorithms are specific in nature, this approach is necessary to ensure that all relevant evidence is identified. Using the EAG's proposed approach, whereby all study designs were limited to *RET*-altered patients with a 2019 date limit, some of the key studies informing the submission would have been missed – for example, the SELECT trial.

Therefore, instead, the Company's SLR approach, which is detailed in Table 1, was considered more appropriate. The current search algorithm has two broad sets. The first set of search terms, line items 1 and 2, were aligned with the EAG's proposed approach, and searched for any study designs, regardless of intervention, for patients with *RET*-altered thyroid cancer.

However, to ensure that all relevant studies were identified, an additional set of search terms (line items 3 and 4 below) were also included, to identify any RCTs for specific interventions of interest, regardless of *RET*-status. These additional searches were necessary to ensure that other, relevant studies in broader TC populations, irrespective of RET status, such as the SELECT trial, were included, due to the paucity of published data for patients with RET-altered thyroid cancer.

Table 1: SLR search algorithms

Search algorithm	Single-arm trials or RCTs in RET tumours (any tumour type, all interventions, any LOT
Line item 1	MTC AND RET AND STUDY DESIGN (REGARDLESS OF TX - RET) – string 18
Line item 2	PTC/DTC AND RET AND STUDY DESIGN (REGARDLESS OF TX - RET) – string 20
Search algorithm	RCTs in MTC/PTC/DTC (any LOT)
Line item 3	MTC AND INTERVENTION AND RCT DESIGN (WITH TX – NO RET) – string 22
Line item 4	PTC/DTC AND INTERVENTION AND RCT DESIGN (WITH TX – NO RET) – string 24

Abbreviations: DTC: differentiated thyroid cancer MTC: medullary thyroid cancer; PTC: papillary thyroid cancer; RCT: randomised controlled trials RET: rearrangements and/or mutations during transfection; SLR: systematic literature review.

b) The first update search reports a search of the Cochrane Library. Subsequent update searches name EBM Reviews (this contains range of resources including Cochrane CENTRAL and CDSR, ACP journal club and the CRD resources DARE, NHS EED etc), please can you confirm which elements are being searched for each of the three update searches.

Lilly can confirm that all the elements within Evidence Based Medicine (EBM) Reviews were searched for the SLR updates.

c) The searches for the 2022 update appear to be missing, please provide.

Full search strategies for the September 2022 clinical SLR update for each electronic database are provided in Table 2–Table 4 below. As noted above, all elements within EBM Reviews were searched, including the Cochrane Library.

Table 2: Medline search strategy for the third clinical SLR update (September 2022)

Search Number	Search Terms	Hits (8th September 2022)
1	exp thyroid neoplasms/	59297
2	((papillary thyroid or thyroid papillary or thyroid papilla) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or microcarcinoma)).mp.	15279
3	((medullary thyroid or thyroid medullary) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or adenoma*)).mp.	6469
4	((Differentiated thyroid or well differentiated thyroid or thyroid follicular or thyroid gland follicular or thyroid follicle or thyroid gland follicle or thyreoideal gland follicle or thyroid gland encapsulated angioinvasive or thyroideal gland encapsulated angioinvasive or thyroideal encapsulated angioinvasive or thyroideal follicle or thyroideal follicular or thyroideal gland follicular) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).mp.	9478
5	(loxo-292 or loxo292 or selpercatinib or loxo 292 or LY3527723 or LY-3527723 or LY 3527723 or RETEVMO or RETSEVMO or pralsetinib or blue-667 or blue 667 or blue667 or BLU 667 or BLU667 or BLU-667 or Gavreto or RET inhibitor or RET inhibitors).mp.	348
6	(cabozantinib or bms 907351 or bms907351 or cabometyx or cabozantinib malate or cabozantinib s malate or cabozantinib smalate or cometriq or xl 184 or xl184).mp.	1419
7	(vandetanib or azd 6474 or azd6474 or caprelsa or vandetinib or zactima or zd 6474 or zd6474).mp.	1058
8	(sorafenib or bay 43 9006 or bay 43-9006 or bay 439006 or bay43 9006 or bay43-9006 or bay439006 or nexavar).mp.	11000
9	(lenvatinib or e 7080 or e7080 or er 203492-00 or er203492-00 or kisplyx or lenvatinib mesilate or lenvatinib mesylate or lenvima).mp.	1658
10	5 or 6 or 7 or 8 or 9	13983
11	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	2183413
12	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	1407659
13	11 or 12	3054013
14	animal/ not (animal/ and human/)	5007607
15	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	4106318
16	14 or 15	8339412
17	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or	5004

	proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	
18	(3 and 17 and 13) not 16	126
19	limit 18 to dt=20210625-20220819	12
20	((2 or 4) and 17 and 13) not 16	49
21	limit 20 to (dt=20210625-20220819)	3
22	(3 and 10 and 11) not 16	79
23	limit 22 to dt=20210625-20220819	5
24	((2 or 4) and 10 and 11) not 16	86
25	limit 24 to dt=20210625-20220819	7

Abbreviations: RET: rearrangements and/or mutations during transfection; SLR: systematic literature review.

Table 3: Embase search strategy for the third clinical SLR update (September 2022)

Search Number	Search Terms	Hits (8th September 2022)
1	exp thyroid neoplasms/	104477
2	((papillary thyroid or thyroid papillary or thyroid papilla) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or microcarcinoma)).mp.	27550
3	((medullary thyroid or thyroid medullary) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or adenoma*)).mp.	12010
4	((Differentiated thyroid or well differentiated thyroid or thyroid follicular or thyroid gland follicular or thyroid follicle or thyroid gland follicle or thyreoideal gland follicle or thyroid gland encapsulated angioinvasive or thyroideal gland encapsulated angioinvasive or thyroideal encapsulated angioinvasive or thyroideal follicle or thyroideal follicular or thyroideal gland follicular) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).mp.	19030
5	(loxo-292 or loxo292 or selpercatinib or loxo 292 or LY3527723 or LY-3527723 or LY 3527723 or RETEVMO or RETSEVMO or pralsetinib or blue-667 or blue 667 or blue667 or BLU 667 or BLU667 or BLU-667 or Gavreto or RET inhibitor or RET inhibitors).mp.	837
6	(cabozantinib or bms 907351 or bms907351 or cabometyx or cabozantinib malate or cabozantinib s malate or cabozantinib smalate or cometriq or xl 184 or xl184).mp.	6094
7	(vandetanib or azd 6474 or azd6474 or caprelsa or vandetinib or zactima or zd 6474 or zd6474).mp.	5316
8	(sorafenib or bay 43 9006 or bay 43-9006 or bay 439006 or bay43 9006 or bay43-9006 or bay439006 or nexavar).mp.	36069
9	(lenvatinib or e 7080 or e7080 or er 203492-00 or er203492-00 or kisplyx or lenvatinib mesilate or lenvatinib mesylate or lenvima).mp.	5091
10	5 or 6 or 7 or 8 or 9	44788
11	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	3039917
12	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	6677077
13	11 or 12	8354272

Search Number	Search Terms	Hits (8th September 2022)
14	animal/ not (animal/ and human/)	1574167
15	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	12146200
16	14 or 15	13520332
17	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	5025
18	(3 and 17 and 13) not 16	486
19	limit 18 to dc=20210625-20220816	55
20	((2 or 4) and 17 and 13) not 16	171
21	limit 20 to dc=20210625-20220816	32
22	(3 and 10 and 11) not 16	234
23	limit 22 to (dc=20210625-20220816)	16
24	((2 or 4) and 10 and 11) not 16	306
25	limit 24 to dc=20210625-20220816	31

Abbreviations: RET: rearrangements and/or mutations during transfection; SLR: systematic literature review.

Table 4: Evidence based medicine reviews search strategy the third clinical SLR update (September 2022)

Search Number	Search Terms	Hits (8th September 2022)
1	exp thyroid neoplasms/	791
2	((papillary thyroid or thyroid papillary or thyroid papilla) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or microcarcinoma)).mp.	410
3	((medullary thyroid or thyroid medullary) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or adenoma*)).mp.	229
4	((Differentiated thyroid or well differentiated thyroid or thyroid follicular or thyroid gland follicular or thyroid follicle or thyroid gland follicle or thyreoideal gland follicle or thyroid gland encapsulated angioinvasive or thyroideal gland encapsulated angioinvasive or thyroideal encapsulated angioinvasive or thyroideal follicle or thyroideal follicular or thyroideal gland follicular) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).mp.	658
5	(loxo-292 or loxo292 or selpercatinib or loxo 292 or LY3527723 or LY-3527723 or LY 3527723 or RETEVMO or RETSEVMO or pralsetinib or blue-667 or blue 667 or blue667 or BLU 667 or BLU667 or BLU-667 or Gavreto or RET inhibitor or RET inhibitors).mp.	35

6	(cabozantinib or bms 907351 or bms907351 or cabometyx or cabozantinib malate or cabozantinib s malate or cabozantinib smalate or cometriq or xl 184 or xl184).mp.	487
7	(vandetanib or azd 6474 or azd6474 or caprelsa or vandetinib or zactima or zd 6474 or zd6474).mp.	281
8	(sorafenib or bay 43 9006 or bay 43-9006 or bay 439006 or bay43 9006 or bay43-9006 or bay439006 or nexavar).mp.	2306
9	(lenvatinib or e 7080 or e7080 or er 203492-00 or er203492-00 or kisplyx or lenvatinib mesilate or lenvatinib mesylate or lenvima).mp.	523
10	5 or 6 or 7 or 8 or 9	3280
11	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	1486958
12	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	730379
13	11 or 12	1577699
14	animal/ not (animal/ and human/)	11271
15	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	137684
16	14 or 15	147080
17	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	98
18	(3 and 17 and 13) not 16	22
19	limit 18 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	44
20	((2 or 4) and 17 and 13) not 16	5
21	limit 20 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	1
22	(3 and 10 and 11) not 16	64
23	limit 22 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	6
24	((2 or 4) and 10 and 11) not 16	135
25	limit 24 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	20

Abbreviations: RET: rearrangements and/or mutations during transfection; SLR: systematic literature review.

d) The same search strategy appears have been used across MEDLINE, Embase and the Cochrane library without translation. The search contains a mix of MeSH and Emtree terms, as well a study design filter which is not

appropriate in Cochrane CENTRAL & CDSR as these are pre-filtered resources. Whilst most of the subject headings appear to have mapped successfully, this may not always be the case and is not recommended. Please consider this advice in any new literature searches.

Lilly thank the EAG for their recommendation.

e) Line #1 contains subject headings for thyroid neoplasms. However, in all searches (MEDLINE, Embase and Cochrane Library) this line appears to have been excluded from all final line combinations. Please explain this omission.

Lilly can confirm that this string was not considered as the focus was on specific histological subtypes of thyroid cancer: medullary thyroid cancer (MTC), papillary thyroid cancer (PTC) and differentiated thyroid cancer (DTC). The alternative algorithm could be to consider thyroid cancer terms in addition to the search terms for MTC, PTC and DTC. Depending on balance between specificity and sensitivity, Lilly deem that it would be acceptable to consider either of these algorithms.

f) Reported search strategies did not contain a final line combining all searches (for Embase see lines #19, #21, 23 and #25). Is this a reporting error, or can the company confirm that results were exported for each of these lines individually?

Lilly can confirm this is a reporting error; all these sets were screened for eligibility.

A 3. Appendix D reported a number of additional searches for both conference proceedings and trials registries which were not fully reported:

a) Conference proceedings – Please provide search terms used and hits per resource.

Lilly can confirm that the search term “Thyroid” was used to search conference proceedings for relevant abstracts. Table 5 presents the number of hits returned per conference proceeding searched for the original clinical SLR (25th September 2019) and subsequent updates. updates carried out in October 2020 (SLR update 1) and September 2022 (SLR update 3).

It should be noted that in the original SLR and updates 1–3, conference proceedings from the last 3 years were searched. SLR update 4, however, covered conference proceedings from the prior three years. Furthermore, the original SLR searched conference proceedings for both thyroid cancer and NSCLC, and search hits were not summarised by indication. Later updates of the SLR were separated by indication and updated to be more disease specific, thus, the original SLR and updates may not be comparable. Therefore, the more recent conference searches should be considered the most relevant.

Table 5: Hits retrieved per conference proceedings resource

Conferences searched	Number of Hits				
	Original SLR	SLR update 1	SLR update 2	SLR update 3	SLR update 4
American Association for Cancer Research (AACR)	0	NA	0	NA	60
American Society of Clinical Oncology (ASCO)	0	NA	24	NA	0
European Society for Medical Oncology (ESMO)	240	NA	17	NA	39
ESMO Immuno-Oncology Congress	0	NA	0	NA	2
European Congress of Endocrinology	0	NA	0	NA	501
American Thyroid Association (ATA) Annual Meeting	0	NA	0	NA	405
European Thyroid Association	0	NA	0	NA	186

Abbreviations: AACR: American Association for Cancer Research; ASCO: American Society of Clinical Oncology; ATA: American Thyroid Association; ESMO: European Society for Medical Oncology; NA: not available.

b) Trials Registries: whilst example search terms are provided it is unclear if these are the complete strategies. If not, please provide complete strategies and hits retrieved for each resource and each search conducted (i.e. including all updates).

The complete search strategy used to search clinical trial registries for the original clinical SLR (25th September 2019) and subsequent updates are presented in Table 6. The accompanying hits retrieved for each resource are provided in Table 7; the number of hits retrieved per clinical trial registry were not available (NA) for the SLR updates carried out in October 2020 (SLR update 1) and September 2022 (SLR update 3).

Table 6: Complete search criteria for clinical trial registries

Condition or disease	• Thyroid
Intervention	• LOXO-292 OR blu667 OR RET OR vandetanib OR cabozantinib OR lenvatinib OR sorafenib

Recruitment status	• Open studies:
	  ○ Recruiting
	  ○ Not yet recruiting
	  ○ Expanded access: available
	  ○ Enrolling by invitation
	  ○ Closed studies:
	  ○ Active, not recruiting
	  ○ Completed
	  ○ Studies with unknown status will not be included

Results	• Studies with available results

Abbreviations: RET: rearrangements and/or mutations during transfection.

Table 7: Hits retrieved per clinical trial registries resource

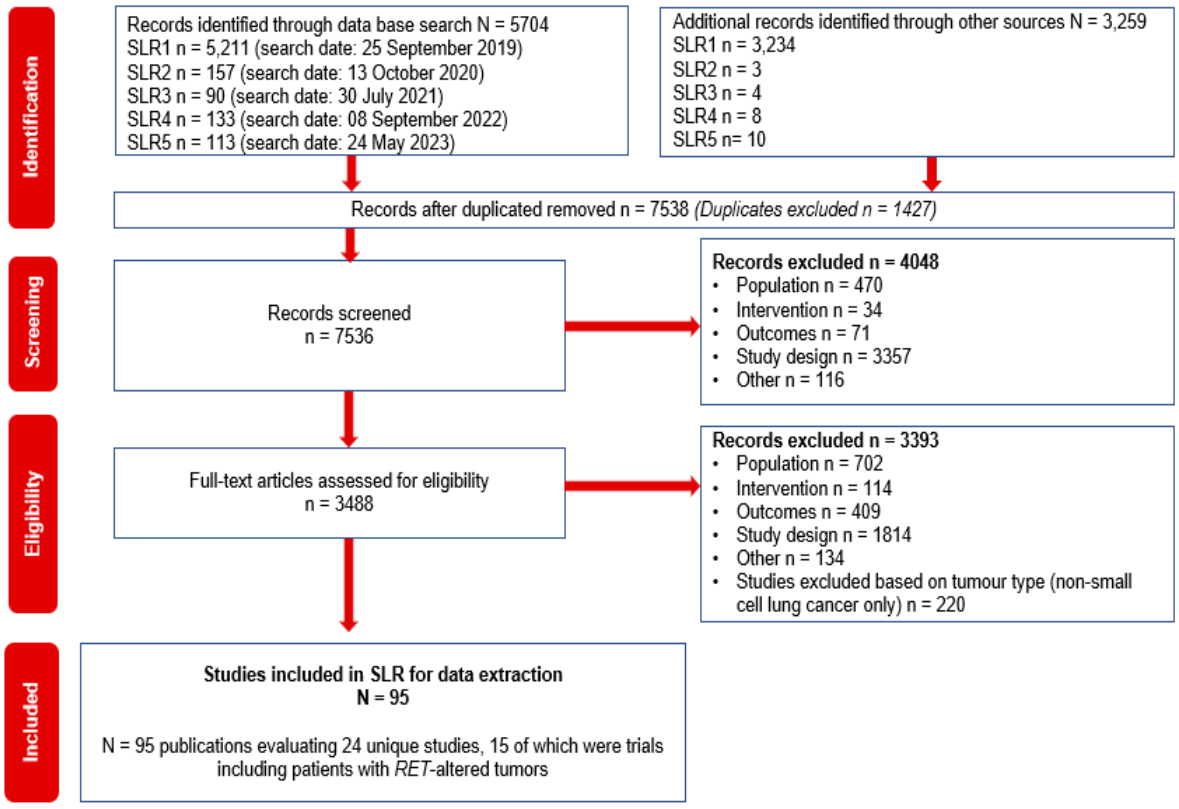
	Number of hits	
	ClinicalTrials.gov	ICTRP
Original SLR	224	22
SLR update 1	NA	NA
SLR update 2	35	9
SLR update 3	NA	NA
SLR update 4	80	0

Abbreviations: ICTRP: International Clinical Trials Registry Platform; SLR: systematic literature review.

A 4. The numbers in the PRISMA flow chart for the update searches 2-4 do not appear to match the totals in the search strategies, it is unclear of this is a reporting error. Please clarify and provide corrected PRISMA flow chart if required.

The numbers presented in Figure 1, Appendix D.1.3 of the CS were incorrect due to a reporting error. The corrected PRISMA flow diagram presenting the results of the clinical SLR, for the *RET*-mutant MTC and *RET* fusion-positive TC populations, is presented in Figure 1.

Figure 1: PRISMA diagram for SLR of clinical trial evidence for selpercatinib and comparators



Abbreviations: NSCLC: non-small cell lung cancer; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RET: rearrangements and/or mutations during transfection; TC: thyroid cancer; SLR: systematic literature review.

A 5. In Appendix G the company stated that "*As thyroid cancer is a rare type of cancer, and there are no other selective RET kinase inhibitors currently available to patients, it was not considered necessary to conduct a SLR to identify relevant previous economic evaluations*". In order to demonstrate the validity of that claim, the EAG would request that the company conduct a full SLR to confirm that there are no relevant economic papers on this topic.

A full economic SLR was unable to be conducted within the timeframe of the clarification questions. However, Lilly maintain that the most relevant economic evaluations were identified by the subsequent targeted literature review (TLR) conducted to support the development of this submission.

Thyroid cancer is a rare type of cancer that accounts for approximately 1% of all new cancer cases in the UK.[1] Currently, there are no other selective RET kinase inhibitors available to patients in UK clinical practice. Therefore, as stated in the in Section B.3.1 and Appendix G.1 of the CS, 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).

Several NICE TAs for patients with TC and MTC were identified as part of a TLR that was conducted in advance of TA742, the original appraisal for selpercatinib in previously treated thyroid cancer; these TAs are presented in Section B.3.1 of the Company submission. In this section, the economic evaluations TA742 and TA928 (cabozantinib for previously treated, advanced DTC) were also noted by Lilly, thus, all economic evaluations relevant to the patient populations covered by this submission published after the original TLR was conducted have been considered in this submission.[2, 3] Specifically, modelling approaches used in this submission are largely based on those taken in TA742, with recognition of the previous appraisal committee's preferences; TA928 is considered less relevant due to the indication being in the (non-*RET* altered) DTC population combined with the fact that cabozantinib was ultimately not recommended in this population.[2]

There have been no recent therapeutic developments in the advanced *RET*-mutant MTC or *RET* fusion-positive TC indications, meaning that it is highly unlikely that an alternative economic evaluation has been subsequently conducted and missed for this submission. Lilly therefore maintain that the original TLR plus the additional TAs identified by Lilly were sufficient to support the development of this submission.

A 6. As stated above, there have been no therapeutic developments in the Appendix H contains a joint HRQoL and cost/resource use studies search conducted in August 2019. Please could the company update this to ensure that no new relevant studies have been published in the five years since this was conducted.

A health-related quality of life (HRQoL) and healthcare cost and resource use (HCRU) use study SLR update was unable to be conducted by Lilly within the timeframe of the clarification questions. However Lilly maintain that the most relevant HCRU and utility data was used to support the development of this submission.

As noted above, thyroid cancer is a rare type of cancer, and there are no other selective RET kinase inhibitors currently available to patients in UK clinical practice. As such, there is a paucity of published HRQoL and HCRU data relating to thyroid cancer, and research into HRQoL and HCRU data for patients with thyroid cancer is not a rapidly evolving field. It is important to note that while the original SLR was conducted in August 2019, since this search, recent relevant NICE appraisals have been subsequently identified and used to identify data that had been accepted by NICE as the best available evidence at the time, to support this submission. Therefore, the most relevant cost/resource use and HRQoL data have been considered during the development of this submission.

It should be considered particularly unlikely that any relevant cost and resource studies have been missed for this submission due to the lack of therapeutic developments in the advanced *RET*-mutant MTC and *RET* fusion-positive TC indications; as no novel treatments have become available for these patients since the publication of TA742, there is no new therapy necessitating a change in practice and management for these patients. This is also particularly low risk in the case of selpercatinib as it is an oral treatment associated with low resource use. As such, the resource use incorporated into the cost-effectiveness model for each population are likely conservative estimates regardless of the sources used.

The lack of therapeutic developments in these populations also justifies why it is considered unlikely that any new utility studies, often conducted to support HTA processes, relevant to these populations have been missed in this submission. In this clarification question response, utility values for the *RET*-mutant MTC and the *RET* fusion-positive TC populations in the economic model have been updated to those derived using EORTC-QLQ-C30 data from the LIBRETTO-001 trial for the any-line *RET* fusion-positive population (subsequently mapped to EQ-5D data). Therefore, even in the unlikely instance that any utility data from the literature were missed for this submission, mapped EQ-5D utility values informing the economic model for this submission have been collected directly from the patient populations of relevance to this submission, in line with the NICE hierarchy of preferred HRQoL methods. As such, the most relevant source of utility data to the patient populations of relevance to this submission have been utilised in the economic model.[4]

A 7. The EAG noticed an error in the search term for utilities in facet 2 of the Embase strategy. In four instances the word "utility" appears to have been replaced by “107tility*”. Please can the company confirm if this was a reporting error, or if this appeared in the searches - and if necessary correct it for the update. Also note that the truncation symbol has been incorrectly applied after the 'y' - if this search was intended to capture the synonym 'utilities' then it should appear after the 't' i.e. utilit*.

Lilly can confirm that this was a reporting error and apologise for this mistake. The correct search terms were used in the search, therefore no update is required.

A 8. Please can you confirm the host for the update database searches reported in Appendix D.

Lilly can confirm that Ovid was used for the clinical SLR update searches.

Decision problem

A 9. **Priority question: Figure 5 in the CS seems to indicate that selpercatinib is currently available for patients with undifferentiated thyroid cancer (TC) as an alternative to full thyroidectomy, according to TA742. However, it is the understanding of the EAG that TA742 recommended selpercatinib only after sorafenib or lenvatinib, which are given to patients with differentiated disease. We note that the NHS England CDF list specifies the following criteria: *"Either the patient has differentiated thyroid cancer (papillary/follicular/Hurtle cell) and has therefore been treated with lenvatinib or sorafenib or the patient has anaplastic thyroid cancer in which case no previous TKI treatment requirement is necessary."* (p. 42)[5] Please clarify that the population in the decision problem (DP) for this appraisal does not include undifferentiated TC. Otherwise, please present any efficacy data available for the subgroup of 4 patients with anaplastic thyroid cancer included in the LIBRETTO-001 trial.**

Following the recommendation of selpercatinib for use within the Cancer Drug's Fund (CDF) (TA742), adults with *RET* fusion-positive anaplastic, or undifferentiated thyroid cancer (ATC) may receive selpercatinib without prior tyrosine kinase inhibitor (TKI; sorafenib or lenvatinib) treatment via the CDF, as patients with ATC are ineligible to receive treatment with lenvatinib or sorafenib.[3, 5]

Since this CDF exit submission is a reassessment of TA742, patients with *RET* fusion-positive ATC should be included in the decision problem for this appraisal, in alignment with the patient populations considered in the original submission (TA742) and currently eligible to receive selpercatinib via the CDF.[3, 5]

The long-term prognosis for ATC is considerably worse than other forms of TC, with five-year survival rates of only 4% for distant ATC.[6] If these patients were no longer able to access selpercatinib, their only alternative option would be palliative treatment with BSC - as such, there is a high unmet need in these patients for continued access to selpercatinib, in line with the current CDF eligibility criteria.

For the *RET*-fusion positive ATC population in in the LIBRETTO-001 trial, efficacy data reporting objective response rate (ORR) and duration of response (DOR) are only available for the prior systemic therapy subgroup (N=4). These data are presented in Table 8 and were broadly consistent with the ORR and DOR results for the prior systemic therapy RET-fusion positive TC population reported in the CS. These results should however be interpreted with caution owing to the small number of patients informing this subgroup analysis.

Table 8: ORR and DOR based on IRC assessment for patients with RET fusion-positive TC in the LIBRETTO-001 trial

	***RET* fusion-positive ATC prior systemic therapy N=4**

ORR	
n (%)	[redacted]
95% CI	[redacted]
DOR (months)	
Median	[redacted]
95% CI	[redacted]

Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DOR: duration of response; IRC: independent review committee; n: number of patients per category; N: number of patients; NE: not estimable; ORR: objective response rate; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[7] Wirth *et al* (2024).[8]

A 10. **Priority question: The decision problem addressed in the CS differs from that specified by the NICE final scope, with respect to population. The NICE final scope specifies: people with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib, and people with advanced *RET* mutation-positive MTC who require systemic therapy after cabozantinib or vandetanib. However, the CS decision problem (DP) specifies: Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib *and/or* sorafenib, and Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib *and/or* vandetanib. Baseline characteristics from the LIBRETTO-001 trial, reported in the CS, indicate that a substantial proportion of participants *RET*-mutant MTC had received prior treatment with *both* cabozantinib AND vandetanib. It also seems possible that some patients with *RET* fusion-positive TC would have received prior treatment with *both* lenvatinib AND sorafenib.**

a) **Please clarify that the populations eligible for selpercatinib and who might receive selpercatinib in clinical practice i.e. the DP population would include those with advanced *RET* fusion-positive who had received *both* sorafenib or lenvatinib TC, and those with advanced *RET* mutation-positive MTC who had received *both* cabozantinib or vandetanib.**

Lilly request that the population wording provided in Table 1 of the CS is updated to:

- Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib **or** vandetanib

- Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib **or** sorafenib

This wording is aligned with the NICE final scope. Clarification on the population wording submitted as part of the original decision problem is provided in response to part A10 b) below.

b) Please clarify that the DP population would include those with advanced *RET* fusion-positive who had only received *either* sorafenib or lenvatinib TC, and those advanced *RET* mutation-positive MTC who had received *either* cabozantinib or vandetanib.

Lilly agree with the positioning for selpercatinib outlined in b), and request that the population wording for selpercatinib be updated to:

- Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib **or** vandetanib
- Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib **or** sorafenib

This is aligned with the current recommendation for selpercatinib, for use within the Cancer Drugs Fund (CDF) for advanced *RET* fusion-positive thyroid cancer in adults who need systemic therapy after sorafenib or lenvatinib, and for advanced *RET*-mutant MTC in people 12 years and older who need systemic therapy after cabozantinib or vandetanib (TA742).[3]

The current recommended wording for selpercatinib as part of TA742 is appropriate because sequential treatment with MKIs for advanced *RET*-altered thyroid cancer following progression is not recommended in the UK – therefore, patients cannot routinely receive lenvatinib and sorafenib, or cabozantinib and vandetanib in UK clinical practice.[5, 9, 10]

Specifically, the CDF listings for lenvatinib and sorafenib confirm that patients must be naïve to both lenvatinib and sorafenib prior to initiating treatment with either MKI, with the exception of early discontinuation (≤ three months) of the prior MKI due to toxicity. Similarly, the CDF listing for cabozantinib specifies that patients must be naïve to cabozantinib and vandetanib prior to initiating treatment, also with the exception of early discontinuation of prior treatment (within ≤3 months) due to toxicity.[5]

Vandetanib was appraised and subsequently not recommended by NICE in 2018 (TA550), meaning that this treatment is not used in UK clinical practice in patients with MTC, regardless of line of therapy.[11] For this reason, as part of TA742, it was agreed that BSC was the only relevant comparator in both patient populations, as patients cannot routinely receive MKIs in the second-line setting in UK clinical practice.[3]

Therefore, the decision problem wording in this submission should be updated to reflect the anticipated use of selpercatinib specifically in the UK, a country in which the sequential use of lenvatinib and sorafenib (*RET* fusion-positive TC) or cabozantinib and vandetanib (*RET*-mutant MTC) is not recommended and is not anticipated to routinely occur in clinical practice.

It should be noted that, in some countries other than the United Kingdom (UK), the relevant MKIs in either populations may be used sequentially upon disease progression. As a result, at the latest DCO of the LIBRETTO-001 trial (13th January 2023 DCO), some patients in LIBRETTO-001 trial had received prior dual treatment with both cabozantinib and vandetanib ([redacted] patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population), along with a minority

of patients in the prior systemic therapy *RET* fusion-positive TC population (4 [9.8%]) who had previously received both lenvatinib and sorafenib.

As a result, the LIBRETTO-001 trial data used in the ITCs and the economic model in both populations includes a subpopulation of dual MKI exposed patients. If anything, this is anticipated to underestimate the efficacy of selpercatinib versus relevant comparators in UK clinical practice, given patients with dual exposure are anticipated to have more advanced disease. This underestimation is supported by the results of the subgroup analyses provided in response to clarification question A.12, which indicate that patients with dual exposure to MKIs are associated with worse efficacy outcomes.

c) Please clarify that in clinical practice those with advanced *RET* fusion-positive who had only received only one of sorafenib or lenvatinib TC would then be eligible to receive the other, and those with advanced *RET* mutation-positive MTC who had received only one of cabozantinib or vandetanib would be eligible to receive the other.

As described in response to part b) above, the sequential use of lenvatinib and sorafenib in patients with advanced *RET* fusion-positive TC following disease progression is not recommended in UK clinical practice.[5]

Additionally, the sequential use of cabozantinib and vandetanib in patients with advanced *RET*-mutant MTC following disease progression is not recommended in UK clinical practice, stated in the National CDF Listings; vandetanib is also not recommended by NICE for the treatment of patients with advanced *RET*-mutant MTC in any-line of treatment in the UK (TA550).[11]

Therefore, patients in UK clinical practice with advanced *RET*-altered thyroid cancer who have received prior treatment with an MKI until disease progression would not subsequently be eligible to receive treatment with another MKI.

d) If what is stated in (c) has been confirmed then, for those with advanced *RET* fusion-positive who had only received only one of sorafenib or lenvatinib TC, please include the other as comparator. For those with advanced *RET* mutation-positive MTC who had received only one of cabozantinib or vandetanib, please include the other as comparator. These comparators should be included in all clinical effectiveness and cost effectiveness analyses.

As described above in b), it is not appropriate to consider the MKIs lenvatinib, sorafenib, cabozantinib and vandetanib as comparators in this submission, which considers selpercatinib as a second-line treatment for *RET* fusion-positive TC and *RET*-mutant MTC for patients who have progressed following prior MKI treatment. MKIs are not recommended by NICE for the treatment of *RET*-altered thyroid cancer in the second-line setting, additionally, vandetanib is not recommended by NICE in any line of treatment for patients with *RET*-mutant MTC.[5, 11] As such, these treatments are not listed in the NICE final scope for this submission as relevant comparators, and there is no rationale to include these treatments in clinical and cost-effectiveness analyses.

Systematic review

A 11. **Priority question: Appendix D1 of the CS states that: *'A systematic literature review (SLR) was conducted to identify clinical trial evidence on the efficacy and safety of selpercatinib and BSC for advanced or metastatic RET-altered MTC and TC.'* However, the reported SLR methods (search strategies and study selection) are not appropriate for maximal identification of data on the efficacy and safety of BSC for advanced or metastatic *RET*-altered MTC and TC. The CS uses the same two studies, as sources for BSC data, as had been previously used in the submission for TA742 (EXAM for the *RET*-mutant MTC population and SELECT for the *RET* fusion-positive TC population) and, as noted in the CS and in TA742, both of these studies have limitations with respect to comparability with the LIBRETTO-001 population and relevance to the decision problem.**

Please conduct an appropriately designed SLR (including literature searches which are not restricted by intervention, see question A1) to ensure, as far as possible, that no better-matched sources of BSC data are available.

As discussed in response to clarification question A1, there are no alternative studies with a placebo/BSC arm in patients with *RET*-mutant MTC or *RET* fusion-positive TC other than the LIBRETTO-001 trial; the search strategy in the clinical SLR informing this submission included all studies in patients with *RET*-altered thyroid cancer regardless of intervention. As such, any other potential studies identified in the thyroid cancer space would be subject to the same key limitations as the EXAM and the SELECT trials.

As discussed in A1, a further SLR has not been conducted, as the SLR update used to inform this submission was sufficiently robust. It is considered extremely unlikely that any studies would have been missed that would provide more relevant evidence for placebo/BSC than the EXAM trial (in the *RET*-mutant MTC population) and the SELECT trial (in the *RET* fusion-positive TC population). As such, the EXAM and SELECT trials informing the ITCs represent the best available sources of evidence for the comparator arms and were deemed acceptable for decision making by the Committee in TA742.[3]

Clinical effectiveness evidence

A 12. **Priority question: Please provide the following further subgroup analyses for the LIBRETTO-001 trial, based on prior systemic therapy:**

a) Patients with *RET* mutation-positive MTC who had been previously treated with EITHER cabozantinib OR vandetanib

Key efficacy endpoints; best overall response (BOR) overall response rate (ORR), duration of response (DOR), progression free survival (PFS) and overall survival (OS), are presented in

Table 9–Table 12 for patients with *RET*-mutant MTC who had previously been treated with either cabozantinib **or** vandetanib, or both cabozantinib **and** vandetanib in the LIBRETTO-001 trial (13th January 2023 DCO).

BOR, ORR, DOR, PFS and OS results for the prior treatment with either cabozantinib **or** vandetanib, or both cabozantinib **and** vandetanib *RET*-mutant MTC populations were [redacted] with the prior cabozantinib/vandetanib *RET*-mutant MTC population, as presented in Table 20–Table 23, Section B.2.6.1 of the CS. As may be expected, response rates were [redacted] in the cabozantinib **or** vandetanib population versus the cabozantinib **and** vandetanib population, along with [redacted]. Rates of OS were [redacted] between the cabozantinib **or** vandetanib n and the cabozantinib **and** vandetanib populations.

As detailed in Section B.1.3.3 of the CS, cabozantinib is the only recommended treatment in the UK MTC (TA516), with vandetanib receiving a negative recommendation from NICE (TA550).[9, 11] Therefore, in UK clinical practice treatment with both cabozantinib and vandetanib is not routinely available to patients with *RET*-mutant MTC. The inclusion of a small proportion of patients who had received prior treatment with both cabozantinib and vandetanib in the *RET*-mutant MTC population in the LIBRETTO-001 trial, may therefore result in the underestimation of the true efficacy of selpercatinib in this population in UK clinical practice.

Table 9: BOR and ORR based on IRC assessment for patients with *RET*-mutant MTC who had previously been treated with either cabozantinib or vandetanib, or with both cabozantinib and vandetanib

	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib** [redacted]	***RET*-mutant MTC prior treatment with both cabozantinib and vandetanib** [redacted]
ORR[a]		
n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
SD16+[b]	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[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).[7]

Table 10: DOR based on IRC assessment for patients with *RET*-mutant MTC who had previously been treated with either cabozantinib or vandetanib, or with both cabozantinib and vandetanib

	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib** [redacted]	***RET*-mutant MTC prior treatment with both cabozantinib and vandetanib** [redacted]
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	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Rate (%) of DOR		
≥12 months (95% CI)	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
DOR follow-up (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[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).[7]

Table 11: PFS based on IRC assessment for patients with *RET*-mutant MTC who had previously been treated with either cabozantinib or vandetanib, or with both cabozantinib and vandetanib

	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib** [redacted]	***RET*-mutant MTC prior treatment with both cabozantinib and vandetanib** [redacted]
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]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Duration of PFS (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥12 months or more (95% CI)	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]
Duration of follow-up (months)		
Median	[redacted]	[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	[redacted]	[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).[7]

Table 12: OS for patients with *RET*-mutant MTC who had previously been treated with either cabozantinib or vandetanib, or with both cabozantinib and vandetanib

	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib** [redacted]	***RET*-mutant MTC prior treatment with both cabozantinib and vandetanib** [redacted]
Duration of overall survival (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; MTC: medullary thyroid cancer; NE: not evaluable; NR: not reported; OS: overall survival; PD: progressive disease; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[7]

b) Patients with *RET* mutation-positive MTC who had been previously treated with BOTH cabozantinib AND vandetanib

Please refer to the response to clarification question A12 part a).

c) Patients with *RET* fusion-positive TC who had been previously treated with EITHER lenvatinib OR sorafenib

Key efficacy endpoints for patients with *RET* fusion-positive TC who had previously been treated with either lenvatinib **or** sorafenib, or with both lenvatinib **and** sorafenib in the LIBRETTO-001 trial (13th January 2023 DCO) are presented in Table 13–Table 16.

BOR, ORR, DOR, PFS and OS results for the prior treatment with either lenvatinib **or** sorafenib *RET* fusion-positive TC population were broadly consistent with the prior systemic therapy *RET*-fusion positive TC population, as presented in Table 26–Table 29, Section B.2.6.2 of the CS.

Given the small sample size of just four patients associated with the BOR, ORR, DOR, PFS and OS results for the prior treatment with both lenvatinib **and** sorafenib *RET* fusion-positive TC population, these subgroup analyses are presented for completeness only and should be interpreted with caution.

Table 13: BOR and ORR based on IRC assessment for patients with *RET* fusion-positive TC who had previously been treated with either lenvatinib or sorafenib, or with both lenvatinib and sorafenib

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib** [redacted]	***RET* fusion-positive TC prior treatment with both lenvatinib and sorafenib N=4**
ORR[a]		
n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
SD16+[b]	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[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; n: number of patients per category; N: number of patients in the population; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 14: DOR based on IRC assessment for patients with *RET* fusion-positive TC who had previously been treated with either lenvatinib or sorafenib, or with both lenvatinib and sorafenib

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib** [redacted]	***RET* fusion-positive TC prior treatment with both lenvatinib and sorafenib N=4**
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	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Rate (%) of DOR		
≥12 months (95% CI)	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
DOR follow-up (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; IRC: independent review committee; N: number of patients; NE: not estimable; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 15: PFS based on IRC assessment for patients with *RET* fusion-positive TC who had previously been treated with either lenvatinib or sorafenib, or with both lenvatinib and sorafenib

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib** [redacted]	***RET* fusion-positive TC prior treatment with both lenvatinib and sorafenib N=4**
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]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Duration of PFS (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥12 months or more (95% CI)	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]
Duration of follow-up (months)		
Median	[redacted]	[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	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IRC: independent review committee; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 16: OS for patients with *RET* fusion-positive TC who had previously been treated with either lenvatinib or sorafenib, or with both lenvatinib and sorafenib

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib** [redacted]	***RET* fusion-positive TC prior treatment with both lenvatinib and sorafenib N=4**
Duration of overall survival (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; MTC: medullary thyroid cancer; NE: not evaluable; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

d) Patients with *RET* fusion-positive TC who had been previously treated with BOTH lenvatinib AND sorafenib

Please refer to the response to Q A.12 part a).

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A 13. The NICE scope lists subgroups of interest as:

- Type of thyroid cancer within advanced *RET* fusion-positive thyroid cancer (such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma)
- Specific type of RET alteration (within *RET* fusion-positive thyroid cancer or *RET*-mutation positive MTC) may need to be considered, as some types of *RET* genetic alteration may be more or less sensitive to selpercatinib

Section B.2.7. provides some of these analyses, for ORR and DOR only and for the prior systemic therapy *RET* fusion-positive thyroid cancer and *RET*-mutation positive MTC populations only. Please provide data for all listed subgroups and for all outcomes available. Please provide these data for all populations used in the

submission: prior systemic therapy *RET* fusion-positive thyroid cancer, prior systemic therapy *RET*-mutation positive MTC, any line *RET* fusion-positive thyroid cancer, and any line *RET*-mutation positive MTC.

Subgroup analyses by TC subtype

Key efficacy endpoints (ORR, DOR, PFS and OS) by subtype of thyroid cancer within advanced *RET* fusion-positive thyroid cancer are provided in Table 17–Table 24 for both the prior systemic therapy and the any-line *RET* fusion-positive TC populations.

Results pertaining to the ATC, Hürthle cell TC and poorly differentiated TC subtypes should be interpreted with particular caution due the particularly small sample sizes associated with each group. Overall, results for ORR, DOR, PFS and OS are broadly aligned with those presented in the CS, particularly for the PTC subgroups which features a larger sample size than other subgroups. However, the interpretations of all results are limited by the associated sample sizes.

Table 17: BOR and ORR based on IRC assessment by type of thyroid cancer within the prior systemic therapy *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=31	Poorly DTC N=5
ORR[a]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a] Response was confirmed by a repeat assessment every ≥28 days.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; IRC: independent review committee; n: number of patients per category; N: number of patients in the population; NA: not applicable; ORR: objective response rate; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[7] Wirth *et al* (2024).[8]

Table 18: BOR and ORR based on IRC assessment by type of thyroid cancer within the any-line *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=54	Poorly DTC N=6
ORR[a]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a] Response was confirmed by a repeat assessment every ≥28 days.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; IRC: independent review committee; n: number of patients per category; N: number of patients in the population; NR: not reported; ORR: objective response rate; PTC: papillary thyroid cancer; RET: rearranged during transfection;TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[7] Wirth *et al* (2024).[8]

Table 19: DOR based on IRC assessment by type of thyroid cancer within the prior systemic therapy *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=31	Poorly DTC N=5
DOR (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DOR: duration of response; DTC: differentiated thyroid cancer; IRC: independent review committee; N: number of patients; NE: not estimable; NR: not reported; PD: disease progression; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 20: DOR based on IRC assessment by type of thyroid cancer within the any-line RET fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=54	Poorly DTC N=6
DOR (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DOR: duration of response; DTC: differentiated thyroid cancer; IRC: independent review committee; N: number of patients; NE: not estimable; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 21: PFS based on IRC assessment by type of thyroid cancer within the prior systemic therapy *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=31	Poorly DTC N=5
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				

Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; IRC: independent review committee; NR: not reported; PD: disease progression; PFS: progression free survival; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 22: PFS based on IRC assessment by type of thyroid cancer within the any-line *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=54	Poorly DTC N=6
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				

≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; IRC: independent review committee; NR: not reported; PD: disease progression; PFS: progression free survival; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 23: OS by type of thyroid cancer within the prior systemic therapy *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=31	Poorly DTC N=5
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; NE: not evaluable; NR: not reported; OS: overall survival; PD: progressive disease; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 24: OS by type of thyroid cancer within the any-line *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=54	Poorly DTC N=6
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; NE: not evaluable; NR: not reported; OS: overall survival; PD: progressive disease; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Subgroup analyses by *RET*-alteration

Subgroup analyses by specific *RET* alteration are provided in Table 25–Table 40, for the *RET*-mutant MTC and the *RET* fusion-positive TC populations respectively. These tables outline results for the prior treatment and any-line patient populations.

RET-mutant MTC population

Rates of ORR for the prior cabozantinib/vandetanib and any-line RET-mutant MTC populations were broadly aligned between subgroup, and median DOR was also aligned between the subgroups, when reached. Median and landmark rates of OS and PFS in both populations were also broadly aligned between subgroups, where reported.

Table 25: BOR and ORR based on IRC assessment by *RET* mutation within the prior cabozantinib/vandetanib *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/La N=8	Other N=21
ORR[b]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
BOR, n (%)				
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SD16+[c]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]	[redacted]
CBR (CR + PR + SD16+[c])[d]				
n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
DCR (CR + PR + SD)[e]				
n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation. [b] Response was confirmed by a repeat assessment every ≥28 days. [c] SD16+ indicates SD lasting ≥16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. [d] 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. [e] 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; n: number of patients per category; N: number of patients in the population; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 26: BOR and ORR based on IRC assessment by *RET* mutation within the any-line *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/La N=14	Other N=38
ORR[b]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
BOR, n (%)				

CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SD16+[c]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]	[redacted]
CBR (CR + PR + SD16+[c])[d]				
n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
DCR (CR + PR + SD)[e]				
n, (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation. [b] Response was confirmed by a repeat assessment every ≥28 days. [c] SD16+ indicates SD lasting ≥16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. [d] 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. [e] 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; n: number of patients per category; N: number of patients in the population; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 27: DOR based on IRC assessment by *RET* mutation within the prior cabozantinib/vandetanib *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/La N=8	Other N=21
Responders (n)	[redacted]	[redacted]	[redacted]	[redacted]
Reason censored (n, %)				
Alive without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
DOR (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of DOR				

≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
DOR follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation.
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),[7] Wirth *et al* (2024).[8]

Table 28: DOR based on IRC assessment by *RET* mutation within the any-line *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/La N=14	Other N=38
Responders (n)	[redacted]	[redacted]	[redacted]	[redacted]
Reason censored (n, %)				
Alive without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
DOR (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of DOR				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
DOR follow-up (months)				

Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation.
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),[7] Wirth *et al* (2024).[8]

Table 29: PFS based on IRC assessment by *RET* mutation within the prior cabozantinib/vandetanib *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/La N=8	Other N=21
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				

Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation. '*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IRC: independent review committee; MTC: medullary thyroid cancer; NR: not reported; PD: disease progression; PFS: progression free survival; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 30: PFS based on IRC assessment by *RET* mutation within the any-line *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/La N=14	Other N=38
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				

Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation. '*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IRC: independent review committee; MTC: medullary thyroid cancer; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 31: OS by *RET* mutation within the prior cabozantinib/vandetanib *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/La N=8	Other N=21
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation. '*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; MTC: medullary thyroid cancer; NE: not evaluable; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 32: OS by *RET* mutation within the any-line *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/La N=14	Other N=38
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				

≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patient has either V804M or V804L mutation. '*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; MTC: medullary thyroid cancer; NE: not evaluable; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

RET fusion-positive TC population

Results for several of the subgroups of the *RET* fusion-positive TC populations should be interpreted with caution due to the small associated sample sizes. Overall, ORR was aligned between subgroups for the prior systemic therapy and the any-line TC populations, while DOR varied between subgroups in both populations. Rates of PFS in each of the prior systemic therapy and the any-line TC populations were broadly similar, while landmark rates of OS did vary between subgroups in both TC populations.

Table 33: BOR and ORR based on IRC assessment by *RET* fusion within the prior systemic therapy *RET* fusion-positive TC population

	CCDC6 N=25	NCOA4 N=8	Other N=7	Unknown N=1
ORR[a]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a] Response was confirmed by a repeat assessment every ≥28 days
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; IRC: independent review committee; n: number of patients per category; N: number of patients in the population; NA: not applicable; NR: not reported; ORR: objective response rate; PTC: papillary thyroid cancer; RET: rearranged during transfection TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[7] Wirth *et al* (2024).[8]

Table 34: BOR and ORR based on IRC assessment by *RET* fusion within the any-line *RET* fusion-positive TC population

	CCDC6 N=40	NCOA4 N=15	Other N=9	Unknown N=1
ORR[a]				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a] Response was confirmed by a repeat assessment every ≥28 days
Abbreviations: CI: confidence interval; IRC: independent review committee; n: number of patients per category; N: number of patients in the population; NR: not reported; ORR: objective response rate; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off),[7] Wirth *et al* (2024).[8]

Table 35: DOR based on IRC assessment by *RET* fusion within the prior systemic therapy *RET* fusion-positive TC population

	CCDC6 N=25	NCOA4 N=8	Other N=7	Unknown N=1
Responders (n)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; IRC: independent review committee; MTC: medullary thyroid cancer; N: number of patients; NE: not estimable; NR: not reported; PD: disease progression; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 36: DOR based on IRC assessment by *RET* fusion within the any-line RET fusion-positive TC population

	CCDC6 N=40	NCOA4 N=15	Other N=9	Unknown N=1
Responders (n)	[redacted]	[redacted]	[redacted]	[redacted]
DOR (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; IRC: independent review committee; N: number of patients; NE: not estimable; NR: not reported; PD: disease progression; RET: rearranged during; transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

Table 37: PFS based on IRC assessment by *RET* fusion within the prior systemic therapy *RET* fusion-positive TC population

	CCDC6 N=25	NCOA4 N=8	Other N=7	Unknown N=1
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IRC: independent review committee; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 38: PFS based on IRC assessment by *RET* fusion within the any-line *RET* fusion-positive TC population

	CCDC6 N=40	NCOA4 N=15	Other N=9	Unknown N=1
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; IRC: independent review committee; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 39: OS by *RET* fusion within the prior systemic therapy *RET* fusion-positive TC population

	CCDC6 N=25	NCOA4 N=8	Other N=7	Unknown N=1
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: CI: confidence interval; NE: not evaluable; NR: not reported; 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),[7] Wirth *et al* (2024).[8]

Table 40: OS by *RET* fusion within the any-line *RET* fusion-positive TC population

	CCDC6 N=40	NCOA4 N=15	Other N=9	Unknown N=1
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				

Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

'*' denotes where some data have been censored.
Abbreviations: ATC: anaplastic thyroid cancer; CI: confidence interval; DTC: differentiated thyroid cancer; NE: not evaluable; NR: not reported; OS: overall survival; PD: progressive disease; PTC: papillary thyroid cancer; RET: rearranged during transfection; TC: thyroid cancer.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Wirth *et al* (2024).[8]

A 14. The CS (Table 2, section B.1.2) gives the recommended dose of selpercatinib based on weight as:

Less than 50 kg: 120 mg orally, twice daily
50 kg or greater: 160 mg orally, twice daily

It appears that all patients included in phase II of the LIBRETTO-001 trial received selpercatinib 160 mg orally, twice daily, and that some patients were included in the LIBRETTO-001 trial (cohorts 1-7) who's body weight was less than 50 kg.

Please confirm that selpercatinib dose, in phase II of the LIBRETTO-001 trial, was not based on weight.

Lilly confirm that dosing in the LIBRETTO-001 trial was not based on body weight. As stated in Section 3.2 of the study protocol, all patients in the Phase II portion of the study received the recommended Phase II dose (RP2D) of selpercatinib (160 mg BID) regardless of body weight. The latest version of the LIBRETTO-001 protocol has been provided alongside this response.[7, 12]

Please provide the numbers of patients in each analysis group (*RET*-mutant MTC prior cabozantinib/vandetanib, *RET*-mutant MTC any-line, *RET* fusion-positive TC prior systemic therapy and *RET* fusion-positive TC any-line) whose baseline body weight was less than 50 kg.

The number of patients in LIBRETTO-001 whose baseline body weight was less than 50 kg within the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations is provided in Table 41. The number of patients whose baseline body weight was less than 50 kg in the prior systemic therapy and the any-line *RET* fusion-positive TC populations is provided in Table 42. Across all cohorts, only a small proportion of patients (<[redacted]) had a baseline body weight of <50 kg.

Table 41: Patients with a body weight less than 50 kg at baseline within the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations in the LIBRETTO-001 trial

	***RET*-mutant MTC prior cabozantinib/vandetanib N=152**	***RET*-mutant MTC any-line population N=295**
Body weight at baseline < 50 kg (n, %)	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; n: number of patients per category; N: number of patients in the population; RET: rearranged during transfection.

Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[7]

Table 42: Patients with a body weight less than 50 kg at baseline within the prior systemic therapy and the any-line *RET* fusion-positive TC populations in the LIBRETTO-001 trial

	***RET* fusion-positive TC prior systemic therapy N=41**	***RET* fusion-positive TC any-line population N=65**
Body weight at baseline < 50 kg (n, %)	[redacted]	[redacted]

Abbreviations: MTC: medullary thyroid cancer; n: number of patients per category; N: number of patients in the population; RET: rearranged during transfection.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023).[7]

Indirect treatment comparison (ITC)

A 15. **Priority question: A MAIC for the comparison of selpercatinib with BSC using LIBRETTO-001 and SELECT was considered infeasible due to lack of trial comparability and small patient numbers in LIBRETTO-001. Given that lack of comparability is the main impetus for population adjustment, notwithstanding the challenges of lack of overlap or small effective sample size (ESS), please conduct a MAIC. Please describe the method including tests of overlap, as specified in NICE DSU TSD 18.**

At the request of the EAG, Lilly have conducted a MAIC for selpercatinib versus BSC using the any-line TC population of the LIBRETTO-001 trial (N=65 patients) and placebo arm of the SELECT ITT population (N=131).

The MAIC adjusted for clinically important baseline characteristics that were known prognostic variables or treatment effect modifiers and that were also reported in both the LIBRETTO-001 trial and the SELECT trial publication (Schlumberger et al. 2015).[7, 13] Specifically, age, sex, ECOG performance status and prior TKI/MKI treatment were prognostic factors adjusted for in the *RET*-mutant MTC population MAIC. Subtype of TC was also adjusted for in this analysis; as noted in Section B.1.3.1 of the CS, outcomes for patients differ substantially between subtype with 5-year survival rates for distant stage papillary thyroid cancer (PTC) and ATC reported as 74% and 4% respectively and therefore it was considered important to adjust for subtype of TC as part of this ITC.[6]

The adjustment of baseline characteristics of the any-line TC population from the LIBRETTO-001 trial, to more closely match the placebo arm of the SELECT ITT population, is summarised in Table 43:

Table 43: Baseline characteristics between the any-line TC LIBRETTO-001 population and the placebo arm of the SELECT ITT population before and after matching

		LIBRETTO-001 any-line TC		SELECT (BSC) N=131
Characteristics	**Category**	**Before weighting N=65**	**After weighting N=[redacted]***	
Age	Mean (SD)	[redacted]	[redacted]	[redacted]
Sex	Male	[redacted]	[redacted]	[redacted]

		LIBRETTO-001 any-line TC		SELECT (BSC) N=131
Characteristics	**Category**	**Before weighting N=65**	**After weighting N=[redacted]***	
ECOG performance status	0 or 1	[redacted]	[redacted]	[redacted]
One prior treatment with a TKI	Yes	[redacted]	[redacted]	[redacted]
Histologic subtype	Papillary	[redacted]	[redacted]	[redacted]
Histologic subtype	Hurthle cell or poorly differentiated	[redacted]	[redacted]	[redacted]

*Effective sample size.
Abbreviations: BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; SD: standard deviation; TC: thyroid cancer; TKI: tyrosine kinase inhibitor.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 DCO).[7] Schlumberger, et al. (2015)[13]

A histogram displaying MAIC weights used in the adjustment is provided in Figure 2. This figure indicates that a substantial proportion of patients in the any-line TC population from LIBRETTO-001 were assigned a weight of 0.0, and were therefore effectively excluded from the analysis, while a very small minority of patients were assigned extremely large weights. This effect substantially increases the uncertainty associated with this analysis, as the results of the MAIC are dependent on the outcomes of the very few patients assigned with sufficiently large weights, with a large proportion of the patient population not considered in the analysis. Accordingly, the effective sample size (ESS) for the any-line TC population of the LIBRETTO-001 trial was just [redacted] following adjustment, indicating the poor overlap between the two trials.

Figure 2: Histogram of MAIC weights for the any-line TC population

Abbreviations: MAIC: matching-adjusted indirect comparison; TC: thyroid cancer.

Results of the MAIC

PFS Kaplan-Meier (KM) data for the placebo arm of the SELECT ITT population, digitised from the Schlumberger et al. 2015 publication, and weighted and unweighted PFS KM data from the LIBRETTO-001 trial (13th January 2023 DCO) are presented in Figure 3.[13] Similarly, OS KM data for the placebo arm of the SELECT ITT population, also digitised from the Schlumberger et al. 2015 publication, and weighted and unweighted OS KM data for the LIBRETTO-001 trial (13th January 2023) are presented in Figure 4. Specifically, the OS data from the SELECT trial was adjusted using rank-preserving structural failure time (RPSFT) model to account for crossover.

The weighted selpercatinib KM curves display increased drops in PFS and OS versus the unweighted curves, which is likely due to the exceeding low number of patients at risk around [redacted] months of follow-up.

Results of the MAIC are presented in Table 44. Before and after weighting, selpercatinib reduced the risk of death compared to BSC by [redacted]% (OS HR: [redacted] [95% CI: [redacted], [redacted]; p<[redacted]]) and [redacted]% (OS HR: [redacted] [95% CI: [redacted], [redacted]; p=[redacted]]), respectively. This result was [redacted] in the unweighted comparison. Additionally, selpercatinib reduced the risk of progression compared to BSC by [redacted]% in the unweighted comparison (PFS HR: [redacted] [95% CI: [redacted], [redacted]; p<[redacted]]) and by [redacted]% in the weighted comparison (PFS HR: [redacted] [95% CI: [redacted], [redacted]; p<[redacted]]). Both of these results were [redacted].

These results should be interpreted with appropriate caution due to the extremely small ESS of the adjusted LIBRETTO-001 population. The adjustment of the LIBRETTO-001 trial population (any-line TC) to more closely match the placebo arm of the SELECT ITT population improved the comparative efficacy of selpercatinib versus BSC in this analysis, which may potentially indicate that unadjusted comparisons are biased against selpercatinib, but these results are strongly limited by the ESS resulting from adjustment.

Figure 3: PFS KM data for selpercatinib (LIBRETTO-001; weighted and unweighted) versus BSC (SELECT)

Abbreviations: BSC: best supportive care; PFS: progression free survival.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 DCO).[7] Schlumberger et al. (2015).[13]

Figure 4: OS KM data for selpercatinib (LIBRETTO-001 trial; weighted and unweighted)

Abbreviations: KM: Kaplan-Meier; OS: overall survival.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 DCO).[7] Schlumberger et al. (2015).[13]

Table 44: MAIC results for OS and PFS (selpercatinib [LIBRETTO-001] versus BSC [SELECT])

	Before weighting			After weighting		
Treatment	Median (95% CI)	HR (95% CI)	p-value	Median (95% CI)	HR (95% CI)	p-value
Overall Survival						
BSC						
Selpercatinib						
Progression-free survival						
BSC						
Selpercatinib						

Abbreviations: BSC: best supportive care; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression free survival.

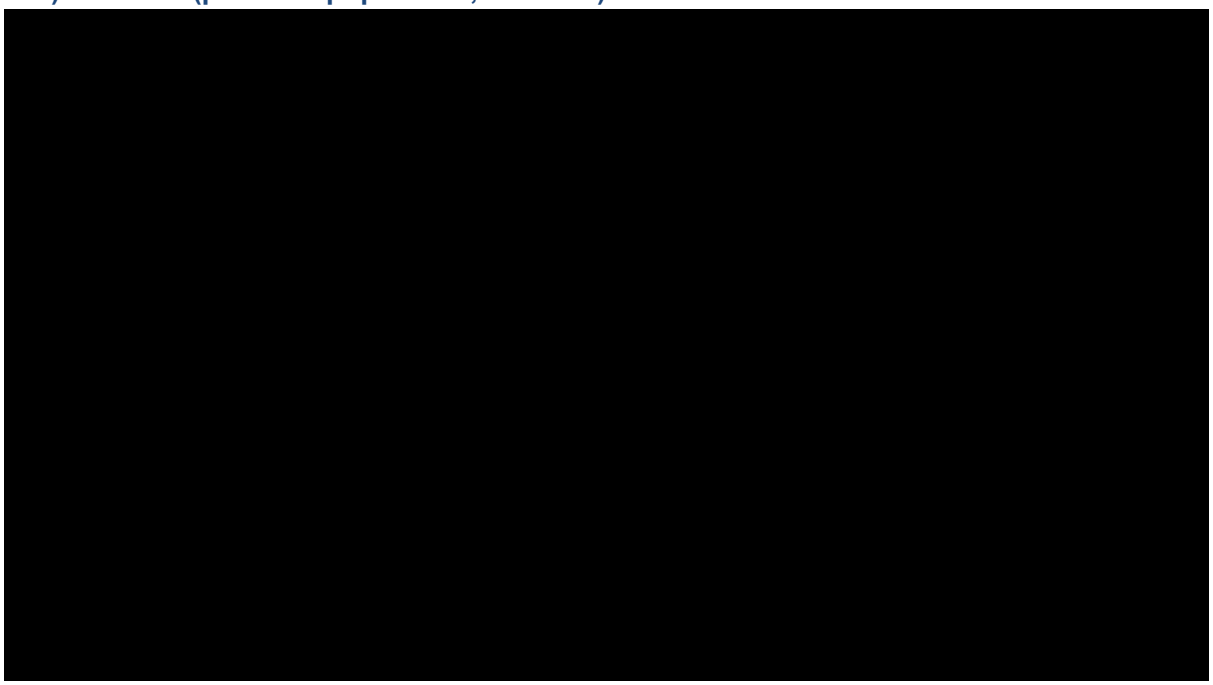
A 16. **Priority question: The OS and PFS ITCs using LIBRETTO-001 and SELECT used the any-line population because data on prior systemic**

therapy were not available for OS. Please conduct an ITC for PFS using the prior systemic therapy population of both trials in order that the effect of prior systemic therapy can be observed.

At the request of the EAG, Lilly have conducted an indirect treatment comparison (ITC) for PFS using the prior systemic therapy TC population of the LIBRETTO-001 trial (N=41) and the subgroup of patients in the placebo arm of the SELECT trial who had received one prior TKI treatment regimen (N=93).[13] A naïve comparison has been used due to the limited overlap between the LIBRETTO-001 and SELECT trial designs and patient populations (as highlighted in Section B.2.9.2 of the CS) and the limited sample size available for the prior systemic therapy *RET* fusion-positive TC population from LIBRETTO-001 (N=41). This is supported by the results of the MAIC presented in response to clarification question A15, for which the ESS of the any-line *RET* fusion-positive TC LIBRETTO-001 trial population (N=65) was reduced to just [redacted] following adjustment. An adjusted comparison between these patient populations was not considered feasible.

PFS KM data for pre-treated patients in the SELECT trial was digitised from the Schlumberger et al. 2015 publication; this is displayed along with the PFS KM data for the prior systemic therapy TC population of the LIBRETTO-001 trial in Figure 5.[13]

Figure 5: PFS KM data for selpercatinib (prior systemic therapy TC population; LIBRETTO-001) and BSC (prior TKI population; SELECT)



Abbreviations: BSC: best supportive care: PFS: progression-free survival; TC: thyroid cancer; TKI: tyrosine kinase inhibitor.

Results of the ITC are presented in Table 45. The ITC indicates that, when assessed in the pre-treated populations of the LIBRETTO-001 trial and the SELECT trial, the risk of progression is reduced by [redacted]% for selpercatinib versus BSC (PFS HR: [redacted] [95% CI: [redacted], [redacted]; p<[redacted]]). Therefore, in addition to demonstrating that selpercatinib results in a [redacted] improvement in PFS versus BSC when comparing the pre-treated patients in either trial, it is important to note that these results are [redacted] with those reported in the CS comparing the any-line TC population of the LIBRETTO-001 trial with the placebo arm of the SELECT ITT population (PFS HR: [redacted] [95% CI: [redacted], [redacted]; p[redacted]]). Therefore, this result provides further

confidence that the ITC presented in the CS for the any-line *RET* fusion-positive TC population of the LIBRETTO-001 trial represents the most appropriate evidence for decision making.

Table 45: Results of the ITC comparing selpercatinib (LIBRETTO-001) versus BSC (SELECT); pre-treated patients

				Treatment vs. Control	
Endpoint	**N[a]**	**Patients with event, n (%)**	**Median PFS (95% CI)[b]**	**HR (95% CI)[c]**	**p-value[c]**
Progression-Free Survival					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]		

Abbreviations: BSC: best supportive care; HR: hazard ratio; ITC: indirect treatment comparison.

A 17. Under key differences in the patient populations, between LIBRETTO-001 and SELECT, the CS lists: *'[redacted]% of patients have advanced or metastatic RET-fusion positive TC in LIBRETTO-001, while no data are reported for a RET-fusion positive subgroup in the SELECT trial.'* – please confirm that, beyond the lack of a RET-fusion positive subgroup, the *RET* fusion status of patients in the select trial is unknown, i.e. it is not known what proportion (if any) of patients in the SELECT trial were *RET* fusion-positive.

The *RET*-fusion status of the patients randomised in the SELECT trial was not reported in the primary manuscript, thus this information is unknown.[13]

Section B: Clarification on cost-effectiveness data

Model structure and comparators

B 1. **Priority. Please provide a table presenting all changes made in this appraisal in comparison with the company approach in TA742, including a summary of the reasoning behind the changes**.

As requested by the EAG, an overview of any changes in the modelling approaches in this appraisal (ID6288) versus TA742, including the justification for any changes, is provided in Table 46.

Table 46: Summary of modelling changes between TA742 and ID6288

<table>
<tr><th>Feature of economic model</th><th>Approach taken in TA742[3]</th><th>Approach taken in ID6288[3]</th><th>Justification for change</th></tr>
<tr><td>Population evaluated by the cost-effectiveness model</td><td>RET-mutant MTC population

The economic model evaluated selpercatinib as a “monotherapy in adults and adolescents 12 years and older with advanced RET-mutant MTC who require systemic therapy”.

RET fusion-positive TC population

The economic model evaluated selpercatinib as a “monotherapy in adults with advanced RET fusion-positive TC who require systemic therapy and who have progressed following prior systemic therapy”</td><td>RET-mutant MTC population

The economic model evaluated selpercatinib “for people aged 12 years and over with advanced RET-mutant MTC who require systemic therapy after cabozantinib or vandetanib”.

RET fusion-positive TC population

The economic model evaluated selpercatinib “for people aged 12 years and over with advanced RET fusion-positive TC who require systemic therapy after sorafenib or lenvatinib”</td><td>Both the RET-mutant MTC and RET fusion-positive TC populations have been updated to reflect the recommendation issued by NICE in TA742: selpercatinib was recommended for use in the CDF in patients who require systemic therapy following lenvatinib or sorafenib (RET fusion-positive TC), or, cabozantinib or lenvatinib (RET-mutant MTC), in line with the criteria for use of selpercatinib outlined in the National CDF List.[3, 5]

The RET fusion-positive TC population considered in the model has been updated to reflect the licence expansion of selpercatinib to people aged 12 years and older, as opposed to just adult patients.[14]</td></tr>
<tr><td>Patient characteristics in the model</td><td>Baseline characteristics used in the model in TA742 were based on the 16th December 2019 DCO of the LIBRETTO-001 trial. These are presented below:

<table><tr><th>Model parameter</th><th>Value</th><th>Source</th></tr><tr><td colspan="3">RET-mutant MTC</td></tr><tr><td>Mean age (SD)</td><td>[redacted]</td><td rowspan="2">LIBRETTO-001 any-line population (n=212)</td></tr><tr><td>Sex (% female)</td><td>[redacted]</td></tr></table></td><td>Baseline characteristics used in the model for this submission were based on the 13th January 2023 DCO of the LIBRETTO-001 trial. These are presented below:
<table><tr><th>Model parameter</th><th>Value</th><th>Source</th></tr><tr><td colspan="3">RET-mutant MTC</td></tr><tr><td>Mean age (SD)</td><td>[redacted]</td><td rowspan="2">LIBRETTO-001 any-line population (n=295)</td></tr><tr><td>Sex (% female)</td><td>39.0%</td></tr><tr><td colspan="3">RET fusion-positive TC</td></tr></table></td><td>The latest DCO of LIBRETTO-001, 13th January 2023, was used to inform the model, given these baseline data are the most mature.

Furthermore, the any-line RET fusion-positive TC population was used in this submission, whereas the prior systemic therapy (N=19) population was used in TA742.

OS KM data were not reported by line of therapy for patients receiving placebo in the SELECT trial. To ensure the populations from LIBRETTO-001 and SELECT were better matched in terms of prior systemic therapy, and for consistency with the approach taken in the RET-mutant MTC population, the TC population used in the model</td></tr>
</table>

	***RET* fusion-positive TC** Mean age (SD): [redacted] — LIBRETTO-001 prior systemic therapy subgroup (n=19) Sex (% female): 52.6% **Abbreviations:** MTC: medullary thyroid cancer; *RET*: rearranged during transfection; TC: thyroid cancer.	Mean age (SD): [redacted] Sex (% female): 50.8% — LIBRETTO-001 any-line population (n=65) **Abbreviations:** MTC: medullary thyroid cancer; *RET*: rearranged during transfection; SD: standard deviation; TC: thyroid cancer.	for this submission was updated to the any-line population. It should be noted that comparisons between the prior systemic therapy *RET* fusion-positive TC population of LIBRETTO-001 and the ITT population receiving placebo in SELECT are anticipated to introduce a bias against selpercatinib. The use of the any-line TC population from the LIBRETTO-001 trial can still be considered as a conservative approach, however; as shown in response to B 3. d), there remains a higher proportion of treatment naïve patients in the placebo arm of the SELECT ITT population than the any-line TC population of the LIBRETTO-001 trial. Therefore, a higher proportion of patients in SELECT had not yet received MKI/TKI treatment and are therefore expected to have a more favourable prognosis than patients who have progressed on prior systemic treatment, with clinicians consulted to support the development of TA742 noting that prior treatment may be considered a prognostic factor.[7, 13, 15]
Intervention and comparators	***RET*-mutant MTC population** Selpercatinib was compared versus cabozantinib and BSC. ***RET* fusion-positive TC population** Selpercatinib was compared versus BSC only.	***RET*-mutant MTC population** Selpercatinib was compared versus BSC only. ***RET* fusion-positive TC population** Selpercatinib was compared versus BSC only.	The comparators in the *RET*-mutant MTC population were updated to BSC only, in line with conclusions of the committee in TA742 that cabozantinib is not a relevant comparator to selpercatinib for patients with *RET*-mutant MTC population who have progressed on prior cabozantinib or vandetanib.[3] This is also in line with guidance provided by the National CDF Listing, which specifically states that selpercatinib may be used in the second-line following lenvatinib **or** sorafenib (*RET* fusion-positive TC) or cabozantinib **or** vandetanib (*RET*-mutant MTC), noting that the sequential use of

			MKIs following disease progression is not funded in UK clinical practice.[5]
Time horizon	A lifetime time horizon of 25 years was used.	A lifetime horizon of 35 years was used.	As part of the ongoing submission for selpercatinib for untreated patients with *RET*-altered thyroid cancer (ID6132), the EAG requested the time horizon of the model be extended to a time until ≤1% of patients in each treatment arm remained alive. A 35-year time horizon was therefore introduced into the model at the clarification question stage of ID6132 to address this request. This time horizon has therefore been used in the model for this submission, ID6288, for consistency, resulting in <2% of patients alive at the end of the time horizon of the model in line with EAG preferences in ID6132.[16]
Clinical parameters and variables			
Clinical data for PFS	***RET*-mutant MTC** Selpercatinib: Weighted KM data generated by the MAIC, using the LIBRETTO-001 any-line MTC population (16th December 2019 DCO) BSC: Unweighted KM data for the *RET*-mutant subgroup receiving placebo (n=62) in the EXAM trial[17] ***RET* fusion-positive TC** Selpercatinib: Unadjusted KM data for the LIBRETTO-001 prior systemic therapy population (n=19) BSC: KM data for the ITT population receiving placebo (n=131) in SELECT[13]	***RET*-mutant MTC** Selpercatinib: Weighted KM data generated by the MAIC, using the LIBRETTO-001 any-line MTC population (13th January 2023 DCO) BSC: Unweighted KM data for the *RET*-mutant subgroup receiving placebo (n=62) in the EXAM trial[17] ***RET* fusion-positive TC** Selpercatinib: Unadjusted KM data for the LIBRETTO-001 any-line population (n=65) BSC: KM data for the ITT population receiving placebo (n=131) in SELECT[13]	In the *RET*-mutant MTC population, PFS for selpercatinib was informed by a MAIC between the LIBRETTO-001 trial for selpercatinib and the EXAM trial for BSC in both submissions. However, data for selpercatinib used in the MAIC was informed by a more recent DCO (13th January 2023) than the original submission (16th December 2019); data informing PFS for BSC in both submissions remained unchanged. PFS data for selpercatinib, informed by the LIBRETTO-001 trial, was updated to the 13th January 2023 DCO. In the *RET*-fusion positive TC population, naïve comparisons of PFS using the LIBRETTO-001 trial for selpercatinib and the SELECT trial for BSC were used in the original and the updated model. However, in this submission the any-line TC population (N=65 patients) in the LIBRETTO-001 trial was used for

			consistency, as OS KM data for a pre-treated population in the SELECT trial are not available. Furthermore, a comparison between the prior systemic therapy *RET* fusion-positive TC population in the LIBRETTO-001 trial and the any-line ITT population receiving placebo in the SELECT trial is anticipated to introduce bias against selpercatinib, with clinical experts consulted as part of TA742 supporting that prior treatment may be considered a prognostic factor for these patients.[13] For these reasons, the any-line TC population of the LIBRETTO-001 trial was used in this submission.
Clinical data for OS	***RET*-mutant MTC** Selpercatinib: Weighted KM data generated by the MAIC, using the LIBRETTO-001 any-line MTC population (16th December 2019 DCO) BSC: Unweighted KM data for the *RET*-M918T subgroup receiving placebo (n=45) in the EXAM trial[18] ***RET* fusion-positive TC** Selpercatinib: Unweighted KM data for LIBRETTO-001 prior systemic therapy population (n=19) BSC: RPSFT-adjusted KM data for patients receiving placebo (n=131) in the ITT population of SELECT, from NICE TA535[10]	***RET*-mutant MTC** Selpercatinib: Propensity score-weighted KM data for the LIBRETTO-001 any-line MTC population (13th January 2023 DCO) BSC: Unweighted KM data for the *RET*-M918T subgroup receiving placebo (n=45) in the EXAM trial[18] ***RET* fusion-positive TC** Selpercatinib: Unweighted KM data for LIBRETTO-001 any-line population (n=65) BSC: RPSFT-adjusted KM data for patients receiving placebo (n=131) in the ITT population of SELECT, from NICE TA535[10]	In the *RET*-mutant MTC population, OS for selpercatinib was informed by a MAIC in both submissions. However, data for selpercatinib used in the MAIC was informed by a more recent DCO (13th January 2023) than the original submission; data informing OS for BSC in both submissions remained unchanged. In the *RET*-fusion positive TC population, naïve comparisons of OS from the LIBRETTO-001 trial were used in the original and the updated model. However, in this submission the any-line TC population (N=65 patients) was used as data for a previously treated population receiving placebo are not available from the SELECT trial.[13] As noted above, the use of the any-line populations in both the SELECT and the LIBRETTO-001 trials is expected to reduce bias.

Survival extrapolation for OS	***RET*-mutant MTC** A stratified gamma extrapolation was chosen for selpercatinib and BSC; no adjustment factor applied ***RET* fusion-positive TC** The piecewise exponential extrapolation was chosen for selpercatinib and BSC; no adjustment factor applied	***RET*-mutant MTC** A stratified Weibull extrapolation was chosen for selpercatinib and BSC; a 2.0 adjustment factor was applied from 5 years onwards in the model. ***RET* fusion-positive TC** The piecewise exponential extrapolation was chosen for selpercatinib and BSC; a 1.2 adjustment factor was applied at 5 years and onwards in the model.	The OS extrapolation for selpercatinib in this submission was informed by an updated data cut (13th January 2023) for the LIBRETTO-001 trial. For the selpercatinib treatment arm, none of the survival extrapolations explored were associated with a substantially improved statistical fit versus the others. Thus, curve selection was informed by alignment with clinical expert values. As no curves lay within the plausible range provided by clinical experts during validation interviews, with all curves lying well above survival estimates at 10 and 15 years, the stratified Weibull curve was selected as the most pessimistic extrapolation which aligned closest to expert estimates. An adjustment factor was then applied to more closely align the survival estimates to clinical expert opinion. In line with recommendations from NICE DSU TSD 14, which notes that the same type parametric model should be fitted to each treatment arm (unless substantial justification can be provided to argue otherwise), the stratified Weibull was also chosen for BSC, with no adjustment factor applied.[19] For the *RET* fusion-positive population, the piecewise exponential extrapolation for selpercatinib and BSC was chosen, as this curve broadly aligned with plausible range provided by clinical experts. An adjustment factor was applied to the extrapolation for selpercatinib OS, to align survival estimates predicted by the model more closely to clinical expert estimates.
TTD	In TA742 (the updated company base case) and this submission (ID6288), TTD was assumed to be equal to PFS plus the length of time observed between progression and treatment discontinuation in the LIBRETTO-001 trial.		TTD data was updated based on the latest DCO of LIBRETTO-001 trial (13th January 2023) which provided the length of time observed between progression and treatment discontinuation for both

	In this submission, PFS and the time between progression and treatment discontinuation was updated in both subpopulations to reflect the data observed from the latest DCO of LIBRETTO-001 (13th January 2023).		the *RET* fusion-positive and *RET*-mutant MTC patient populations.
Adverse event frequency	**_RET_-mutant MTC and _RET_ fusion-positive TC** Grade ≥3 AEs with at least 2% difference in frequency between all interventions in the comparator trials were included in the model. AE data for selpercatinib in TA742 were based on the *RET*-mutant MTC SAS (N=299) of the 16th December 2019 DCO for both the *RET*-mutant MTC and the *RET* fusion-positive TC populations.	**_RET_- mutant MTC and _RET_ fusion-positive TC** In error, the same approach was for AEs was used in the model for this submission; Grade ≥3 adverse events with at least 2% difference in frequency between all interventions in the comparator trials were included in the model, yet only AEs for selpercatinib and BSC are relevant for this submission. Please see the response to B6 for further details. AE data for selpercatinib in this submission was updated to be based on the 13th January 2023 DCO. The *RET*-mutant MTC SAS DCO (N=324) was used to inform AEs for the MTC population, and the *RET* fusion-positive TC SAS (N=66) was used to inform AEs for the TC population.	The most recently available clinical data for selpercatinib from the LIBRETTO-001 trial, the 13th January 2023 DCO, was used to inform AEs included in the model for ID6288. The *RET* fusion-positive TC SAS population was a sufficient size at the 13th January 2023 DCO to inform AEs for the TC population, thus, separate safety data were used for the TC and MTC patient populations of relevance to this submission. Data informing adverse event frequency for BSC in the model was unchanged between submissions: AE frequencies were informed by the EXAM trial for MTC and the SELECT trial for TC, respectively.[13, 18]
Health-related quality of life			
Health state utility values	**_RET_ mutant-MTC and _RET_ fusion-positive TC** HSUVs in TA742 were modelled to be treatment independent, and were based on the Fordham et al. 2015 vignette study in radioactive iodine-refractory DTC.[20]	**_RET_ mutant-MTC and _RET_ fusion-positive TC** The Fordham et al. 2015 vignette study in radioactive iodine-refractory DTC was initially used to inform utility values in this submission. However, the updated base case submitted alongside this response incorporates EORTC-QLQ-C30 data from the LIBRETTO-001 any-line *RET* fusion-positive TC population, which has been mapped to	In line with committee preferences for the ongoing appraisal for selpercatinib in the first-line thyroid indication (ID6132), utility values have been updated from the Fordham et al. 2015 health state utility values to utility values mapped from EORTC-QLQ-C30 data collected from the any-line TC population from the LIBRETTO-001 trial (13th January 2023 DCO). ID6132 also models the any-line patient populations for *RET*-mutant MTC and *RET* fusion-positive TC, thus, this approach was chosen for consistency.

		EQ-5D data using the Young et al. 2015 mapping algorithm.[21]	
Adverse event utility decrements	***RET* mutant-MTC and *RET* fusion-positive TC** Utility decrements for specific AEs were used, where available. When no specific utility values were available, the same utility decrement (−0.11) was applied for all AEs based on Beusterien *et al.* (2009), in line with TA615. Specific AE decrements for the TC population were identified for diarrhoea (0.38) and fatigue (0.08), from TA535. Thus, these values were used in the model.		The approach used between the models is aligned, the frequencies of each specific AE do however vary between the models (see above).
Drug acquisition costs			
Costs of treatments in the model	Selpercatinib: A PAS discount of [redacted] was applied to selpercatinib during the post-submission stages of this appraisal.	Selpercatinib: The PAS discount applicable to selpercatinib has since been updated to [redacted]	The PAS discount for selpercatinib has been revised since TA742, providing a [redacted] to the NHS.
Relative dose intensity	***RET* mutant-MTC and *RET* fusion-positive TC** For selpercatinib, no dose reductions were applied in the first treatment cycle in either the TC or MTC populations. In subsequent treatment cycles, the mean dose intensity observed in the LIBRETTO-001 trial for the *RET*-mutant MTC SAS ([redacted]%; N=[redacted]) at the 16th December 2019 DCO was used to account for selpercatinib dose reductions.	***RET* mutant-MTC and *RET* fusion-positive TC** For selpercatinib, no dose reductions were applied in the first treatment cycle in either the TC or the MTC populations. In subsequent treatment cycles, the mean dose intensity observed in the LIBRETTO-001 trial for the *RET*-mutant MTC SAS ([redacted]%; N=324) and the *RET* fusion-positive TC SAS ([redacted]%; N=66) at the 13th January 2023 DCO was used to account for selpercatinib dose reductions in each respective population.	The latest DCO for LIBRETTO-001 trial, 13th January 2023, was used to inform relative dose intensity in the model for this submission. At this DCO, the *RET* fusion-positive TC SAS was of sufficient sample size to inform the relative dose intensity for the TC population in the model, therefore, relative dose intensity data incorporated into the model were informed by separate populations from LIBRETTO-001.
Resource use costs	***RET* mutant-MTC and *RET* fusion-positive TC**	***RET* mutant-MTC and *RET* fusion-positive TC**	While the assumptions used in both models are aligned, the costs for resource use in this submission were updated to the most recently

	Resource use types and frequencies were derived from TA516; associated costs were derived from NHS National Cost Collection 2018/2019 data.[22]	Resource use types and frequencies were derived from TA516; associated costs were derived from NHS Reference Costs 2021/2022.[23]	available data (NHS Reference Costs 2021/2022).[23]
Adverse event costs	***RET* mutant-MTC and *RET* fusion-positive TC** Costs were informed by the NHS National Cost Collection database 2018/19. Cost codes used were based on TA516 or assumptions.	***RET* mutant-MTC and *RET* fusion-positive TC** Costs were informed by the NHS Cost Collection database 2021/22. Cost codes used were based on TA516 or assumptions.	Reference costs were updated to the most recently available publication from NHS England in this submission.
Decision modifiers	The appraisal committee concluded that selpercatinib did not meet end of life criteria in either the *RET*-mutant MTC or *RET* fusion-positive TC population, but noted the data supporting this decision were highly uncertain.[3]	Results of the QALY shortfall analysis in this submission (Section B.3.6 in the CS) indicate that selpercatinib is eligible for a 1.2 severity modifier when compared with BSC in both the *RET*-mutant MTC and the *RET* fusion-positive TC populations.	At the time of TA742, the severity modifier framework had not yet been introduced by NICE. The end-of-life framework has since been discontinued by NICE.

Abbreviations: AE: adverse event; BSC: best supportive care; CDF: Cancer Drugs Fund; DCO: data cut off; DSU: Decision Support Unit; DTC: differentiated thyroid cancer; EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; HSUV: health state utility values; ITT: intention-to-treat; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; NICE: National Institute of Health and Care Excellence; OS: overall survival; PFS: progression free survival; QALY: quality-adjusted life year; RET: rearranged during transfection; SAS: safety analysis set; TA: technology appraisal; TC: thyroid cancer; TKI: tyrosine kinase inhibitor; TTD: time to treatment discontinuation.

B 2. In the CS it is stated that a time horizon of 35-years has been used in the current submission as compared to the 25-year time horizon used in TA742 (also in Table 53 of the CS). However, in the electronic model it seems that a 25-year time horizon has been used in the company base case analysis (for both populations). Please confirm if this is an error in the model or an error in the report and make the appropriate corrections. If time horizon should be 35-years, please update all company results using the 35-year time horizon.

Lilly would like to highlight that when results are run in the submitted model, the time horizon automatically resets to 25 years. As such, while the submitted model implies that a 25-year time horizon was used to generate results, Lilly can confirm that the results presented in the CS are based on a 35-year time horizon, as described in the CS. As such, neither the wording nor the results presented in the submission require updating. Lilly can also confirm that the updated cost-effectiveness results presented throughout this clarification questions response continue to be based on a 35-year time horizon.

Clinical effectiveness

B 3. **Priority. Different stratified and unstratified parametric models to fit the OS and PFS data for selpercatinib versus BSC. On page 128 of the CS it is stated that '***to more closely align the landmark rates of OS for selpercatinib with the estimates provided by clinical experts during interviews conducted to support ID6132, an adjustment factor was applied to the selected MTC (2.0 adjustment factor) and TC (1.2 adjustment factor) selpercatinib OS curves from 5 years onwards***.'**

a) **Please confirm if the company's preferred model selection for the OS of selpercatinib for *RET*-mutant MTC patients (stratified Weibull) and RET fusion-positive TC population (piecewise exponential) was mainly driven by the fact these two models presented the lowest 10- and 20-year survival estimates as compared to all other parametric models (considering the AIC/BIC scores were comparable between models).**

Lilly can confirm that, as Akaike information criterion (AIC)/ Bayesian information criterion (BIC) scores were similar between all parametric models, then the selection of the most appropriate extrapolations to model OS for selpercatinib was informed by plausible long-term estimates of survival provided by UK clinical experts.

Based on these estimates, for *RET*-mutant MTC patients, the stratified Weibull extrapolation was selected to model OS for selpercatinib. Lilly acknowledge that all extrapolations explored

overestimate survival versus estimates provided by the UK clinical experts; however, the most pessimistic OS curve for selpercatinib, the stratified Weibull, aligns most closely with these estimates. The use of the stratified Weibull curve aligns with the preferred assumptions of the Committee in the original appraisal of selpercatinib in advanced *RET*-altered MTC and TC (TA742) for patients previously treated with systemic therapy, which was based on an earlier data cut of the same population of LIBRETTO-001 used to inform the efficacy of selpercatinib in this appraisal. The appraisal Committee in TA742 noted that the stratified Weibull and stratified gamma curves were the most clinically plausible survival extrapolations.[3]

When assessing OS extrapolations explored for selpercatinib in the *RET* fusion-positive TC population, it was found that all curves that predicted survival rates within clinical expert estimates at 10 years overestimated survival at 20 years (see Table presented in response to Question B3e). Similarly, the two curves that predicted survival rates within clinical expert estimates at 20 years underestimated survival at 10 years. None of the survival extrapolations for selpercatinib OS, which are correctly reported in Table 49 of this response document, produce clinically plausible estimates at all timepoints provided by clinical experts during validation to support the first-line thyroid submission for selpercatinib, ID6132.[16] As such, it was necessary to select a single curve and apply an adjustment factor to generate plausible landmark survival estimates – an approach that was considered appropriate for decision making in the draft guidance available for ID6132.[16] In the absence of any clear rationale to select one curve over the other, the piecewise exponential extrapolation was chosen for this population in recognition of committee preferences in TA742.[3] As shown by Table 49, application of the 1.2 adjustment factor after 5 years aligned landmark survival rates to clinical expert estimates.

b) Please confirm if adjustment factors for the OS hazard rates of both populations were in principle used because all alternative parametric models presented in Table 61 for the *RET*-mutant MTC population and Table 67 for the RET fusion-positive TC population were predicting higher 10- and 20-year survival estimates than the company's preferred models. And is it correct that, based on the clinical experts' feedback, usage of an alternative parametric model was not expected to perform any better than the company's preferred models, and therefore adjustment factors were deemed to be the most appropriate alternative option to get model predictions that align with clinical expectations?

This is correct. As previously detailed in B 3. a), none of the survival extrapolations for either *RET*-mutant MTC or *RET* fusion-positive TC provided clinically plausible estimates of survival at both 10 and 20 years, as provided by clinical experts consulted to support the development of the first-line thyroid submission for selpercatinib, ID6132.[24] Therefore, the application of an adjustment factor was necessary in order to generate curves that aligned with clinical expectations. To achieve this, Lilly applied adjustment factors of 2.0 and 1.2 from 5 years and onwards for the *RET*-mutant MTC and the *RET* fusion-positive TC populations, respectively.

c) **Please explain if independent parametric models would be expected to perform differently in terms of clinical plausibility than the stratified model analyses.**

Independent and stratified parametric models may be associated with different probabilities of survival. Lilly have conducted parametric survival modelling using flexsurvreg function in R, which considers the use of both stratified and independent parametric models. For example, considering the stratified Weibull extrapolation as an example (denoted Model A), the survival analysis produces estimates for Shape, Scale, Treatment and Shape for the Treatment parameters. However, when fitting an independent parametric Weibull model (denoted Model B), data are restricted to only one treatment category (reference category in Model A), estimates are only obtained for shape and scale parameters. The estimates of shape and scale parameter from Model A and Model B are the same; however, in Model B, the estimates for Treatment and shape for Treatment are not estimated. As a result, the final survival probabilities predicted from Model A versus Model B may differ.

This can be seen throughout the Company submission, where the results of both independently fitted and stratified models have been presented throughout Section B.3.3, and the selection of the most appropriate extrapolation in each case considered both stratified and independently fitted models.

d) **OS and PFS data for the MTC population (n=295) in the economic model were based on 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)." OS and PFS data for the TC population (n=65) were pooled using patients with *"TC in the LIBRETTO-001 trial who were systemic therapy naïve (with the exception of radioactive iodine therapy) (n=24) or patients with TC that had previously received systemic therapy (n=41)."***

Given the above sub-questions, it can be concluded that the alternative parametric models seem to lead to clinically implausible OS predictions for both populations when no adjustment factors are used. This limitation is also recognised by the company in section B.3.15.2 where it is stated that '*the use of the any-line populations for MTC and TC will slightly overestimate OS and PFS for selpercatinib, compared with the prior systemic therapy population for MTC and TC, which represent the populations of interest for this submission.***' A similar bias caused by using any-line populations might pertain to the OS and PFS estimates of BSC but that would also depend on the share of the naïve patients in**

each arm.

- Please explain if the share of treatment-naïve patients in the selpercatinib OS/PFS data would be the same as in the OS/PFS data for the BSC arm.

The proportion of patients with MTC or TC in the LIBRETTO-001, EXAM and SELECT trials that that had not received prior MKI or TKI therapy at baseline are presented in Table 47 and Table 48. A lower proportion of patients with MTC or TC had not received prior MKI/TKI therapy in the LIBRETTO-001 trial (MTC: [redacted]; TC [redacted] than in the placebo arms of the EXAM (77.5%) and SELECT (79.4%) trials, respectively. As noted in the CS, prior MKI/TKI treatment is considered a prognostic factor for *RET*-altered MTC and TC, with treatment-naïve patients associated with an improved prognosis. Therefore, the observed share of treatment-naïve patients across the LIBRETTO-001, EXAM and SELECT trials may bias results against selpercatinib.

Table 47: Prior MKI/TKI therapy status of patients with MTC in the in the LIBRETTO-001 and EXAM trials

	LIBRETTO-001 *RET*-mutant MTC any-line population[a] (N=295)	EXAM Placebo (N=111)
Received prior MKI/TKI therapy, n (%)		
No	[redacted]	86 (77.5)

[a] The MTC any-line population includes the MTC: Cab/VanNaïve and the MTC: Cab/Van populations.
Abbreviations: Cab: cabozantinib; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; N: number of patients in population; n: number of patients; RET: rearranged during transfection; TKI: tyrosine kinase inhibitor; Van: vandetanib;.
Source: Raez et al (2023),[25] Elisei, et al (2013).[26]

Table 48: Prior MKI/TKI therapy status of patients with TC in the in the LIBRETTO-001 and SELECT trials

	LIBRETTO-001 *RET*-fusion positive TC any-line population[a] (N=65)	SELECT Placebo (N=131)
Received prior MKI/TKI therapy, n (%)		
No	[redacted]	104 (79.4%)

[a]The TC any-line population includes the TC:TrtSysNaïve and the TC:TrtSys populations.
Abbreviations: MKI: multi-kinase inhibitor; N: number of patients in population; n: number of patients; RET: rearranged during transfection; TC: thyroid cancer; TKI: tyrosine kinase inhibitor.
Source: Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023),[7] Schlumberger et al (2015).[13]

- Please conduct all survival analyses (OS and PFS, including model selection based on AIC/BIC, visual assessment and clinical plausibility) for selpercatinib by using only the patient population who had previously received systemic therapy. Please incorporate these results into the economic model and run a scenario analysis with those.

Due to comparator data availability, it is not considered appropriate to conduct survival analyses using the prior systemic therapy populations of the LIBRETTO-001 trial and include these results as a scenario analysis in the cost-effectiveness model.

In the *RET*-mutant MTC population, the EXAM trial is used to inform PFS and OS for BSC using the *RET*-mutant subgroup of the placebo arm as a proxy. PFS and OS KM data for this trial are not reported by line of therapy, therefore, as presented previously in response to part d) above, the PFS and OS KM data for the placebo arm of the trial are provided by a population for which 77.5% of patients had not received a prior MKI/TKI therapy. Individual patient level data (IPD) are only available for the LIBRETTO-001 trial, and not the EXAM trial. Since all patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population in the LIBRETTO-001 trial had received a prior MKI, it would be impossible to adjust for prior treatments using IPD from LIBRETTO-001 and aggregate data from the EXAM trial in a MAIC.

Therefore, a large imbalance between the prior systemic therapies received by patient populations in the two trials would exist in this comparison. This is expected to substantially bias results against selpercatinib; the LIBRETTO-001 trial population informing the MAIC would include a higher proportion of patients who had already progressed on prior systemic therapy versus the EXAM trial. These patients would likely face poorer outcomes than those naïve to systemic therapy, supported by clinical validation collected for the original submission for selpercatinib in this indication (TA742) in which clinical experts stated that prior therapy may be considered a prognostic factor.[15] As such, a MAIC between the prior cabozantinib/vandetanib *RET* mutant-MTC population of the LIBRETTO-001 trial and the any-line *RET*-mutant placebo arm of the EXAM trial would be associated with a substantial bias against selpercatinib treatment and would therefore not be suitable for decision making. As such, Lilly have not conducted this analysis.

The same argument applies for conducting survival analyses using the prior systemic therapy *RET* fusion-positive TC population of LIBRETTO-001; PFS KM data for the pre-treated subgroup in the placebo arm of the SELECT ITT population are available, but OS KM data are not available by line of therapy for these patients. It is not appropriate to model PFS and OS based on different populations, thus the placebo arm of the SELECT ITT population would still be used to inform PFS and OS in the model. As shown in B 3. , this would result in a comparison in which a substantially higher proportion of patients in the LIBRETTO-001 trial would have previously progressed on prior MKI/TKI treatment versus the SELECT trial. This patient population would therefore face poorer outcomes, as prior treatment is considered as a prognostic factor. As such, a comparison against the prior systemic therapy *RET* fusion-positive TC population of LIBRETTO-001 against the any-line placebo arm of the SELECT ITT population is anticipated to result in a substantial bias against selpercatinib and would not be suitable for decision making. As such, Lilly have not conducted the requested analyses.

e) In Table 67, the median and landmark survival predictions for the piecewise exponential with adjustment factor (1.2) are higher than those for the piecewise exponential without the adjustment factor. Please confirm if this is an error and indicate whether the error occurs in the model, or only is a typo in the report. If the former, please provide a corrected model, if the latter, please provide a corrected version of Table 67.

Lilly would like to thank the EAG for highlighting this discrepancy, which is due to a reporting error identified in the CS relating to the landmark OS estimates predicted by the piecewise exponential curve for selpercatinib in TC reported in Table 67, Section B.3.3.4 of the CS. The median and the 5-, 10- and 20-year survival estimates reported for the piecewise exponential curve were reported incorrectly; the correct version of this table is provided in Table 49 below.

As the survival estimates for the piecewise exponential adjustment factor *with* the 1.2 adjustment factor applied after 5 years were reported accurately in the submission, the submitted model reflects the correct values for selpercatinib OS and no updates to the company base case are required in response to this reporting error.

Table 49: Corrected 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]
(Corrected) piecewise exponential	[redacted]	[redacted]	[redacted]	[redacted]
Median and landmark survival with adjustment factor applied				
Piecewise exponential (1.2 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Parametric curves are ordered from highest to lowest 10-year survival.
Abbreviations: NA: not applicable; OS: overall survival; *RET*: rearranged during transfection; TC: thyroid cancer.

B 4. To inform the OS for BSC, the company used KM data from RET M918T-positive subgroup treated with placebo (n=45) of the EXAM trial. The company argued that ‘as part of TA742, UK clinical experts confirmed that placebo outcomes in the RET M918T-positive group may be similar to the RET-mutant

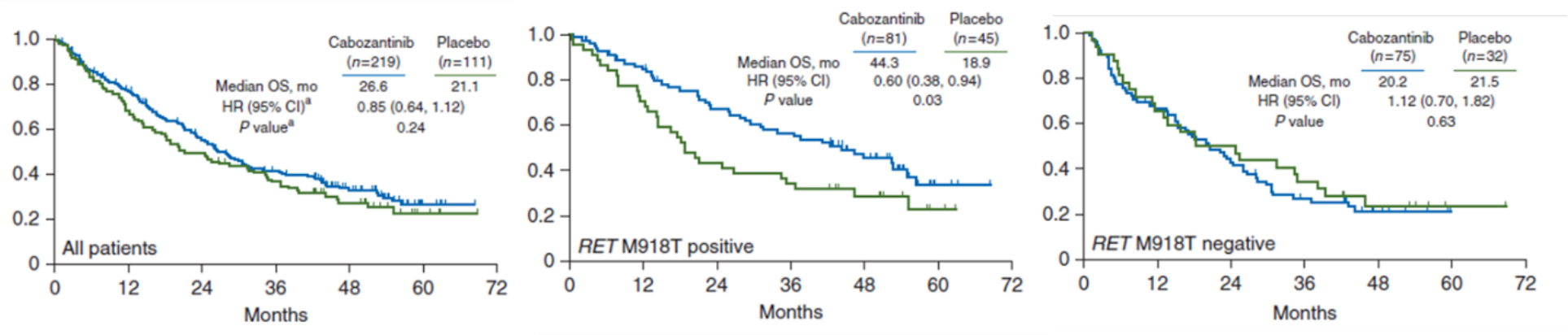
group as a whole.' However, the EAG in the original submission expressed concerns about the use of the *RET*-M918-positive group as M918 status could be a prognostic factor which can indicate a worse OS for the *RET*-M918-positive group than for the *RET*-mutant group. Please explain if an exhaustive search has been conducted to find another source of data, e.g. RCTs or registries, that could more appropriately inform the OS of the BSC arm.

Lilly would firstly like to refer to the response to clarification question A1, which provides clarity on the searches used to identify relevant data for *RET*-mutant MTC and *RET* fusion-positive TC in the clinical SLR. The searches included all studies recruiting patients with *RET*-altered thyroid cancer, regardless of interventions and therefore all directly relevant studies investigating placebo/BSC in this population would have been captured. As noted in response to A1, the only studies that may not have been captured in the SLR are single-arm studies or RCTs including a placebo/BSC arm that did not explicitly include patients with *RET*-altered thyroid cancer, and it is extremely unlikely that any evidence that would be more relevant than the SELECT or EXAM trials, that were also accepted as part of TA742, would have been omitted, given the paucity of other treatment options for patients with thyroid cancer.

Lilly recognise the concerns raised by the EAG in the original submission (TA742) pertaining to the *RET* M918T-positive status of patients treated with placebo in the EXAM trial. However, as demonstrated in Figure 6 below, *RET* M918T status had a minimal impact on efficacy outcomes in the placebo arm of the EXAM trial, with median OS changing minimally based on *RET* M918T status (21.5 vs 18.9 in the *RET* M918T positive versus *RET* M918T negative subgroups, respectively). *RET* M918T status had a far more pronounced impact on the cabozantinib arm of the EXAM trial (44.3 versus 26.6 months, respectively), likely due to the mechanism of action of cabozantinib, a treatment which targets RET, as a multi-kinase inhibitor. However, this is not applicable to BSC. Thus, any potential concerns relating to the use of the *RET* M918T-positive subgroup of the placebo arm should be considered negligible, and are unlikely to introduce any uncertainty into the submission.

Further, Lilly's decision to select the *RET* M918T-positive subgroup in the EXAM trial was guided by clinical expert opinion, which indicated that outcomes for these patients receiving BSC could be considered similar to the general *RET*-mutant MTC population. As such, Lilly maintain that the best source of evidence for BSC/placebo in this population is the RET M918T-positive subgroup of the placebo arm of the EXAM trial.

Figure 6: OS KM data by RET M918T status in the EXAM trial



Abbreviations: CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival; RET: rearranged during transfection.
Source: Schlumberger et al. (2017).[18]

B 5. **Priority. In the base case for both the RET-mutant MTC and RET fusion-positive TC populations, TTD for selpercatinib is assumed equal to PFS, with the addition of the mean time from progression to treatment discontinuation (11 weeks for MTC and 14 weeks for TC). It was noted that this approach aligned with the EAG's preferred approach in TA742 as attempts to estimate a parametric curve for TTD led to implausible results. However, the survival data in TA742 were different, i.e. from an earlier data cut, than the currently available data. So, please conduct a complete survival analysis for the TTD data of selpercatinib for both populations. Please consider AIC/BIC, visual assessment, and clinical plausibility in your response. Based on the preferred model selection please run a scenario analysis. In case the survival results are clinically implausible as argued in TA742 please provide a detailed explanation on the reasons why these would be considered clinically implausible.**

Lilly would like to clarify that the economic model submitted alongside the CS already includes the functionality to base TTD for selpercatinib on data from the LIBRETTO-001 trial for both the any-line TC and MTC patient populations.

This model functionality can be located in the 'Survival – TC' tab and the 'Survival – MTC' tab for the *RET* fusion-positive TC and *RET*-mutant MTC populations, respectively. In the *RET* fusion-positive TC sheet, a separate survival extrapolation is available for TTD, and each parametric function may be applied to selpercatinib and comparator TTD KM curves, as these data were available for all treatments. In the RET-mutant MTC sheet, TTD based on KM data may be selected for selpercatinib only, listed in the same graph as PFS and are able to be selected using cell D36.

However, Lilly have not incorporated TTD based on LIBRETTO-001 TTD data in the economic model in recognition of the appraisal committee's preferences in ID6132, which accepted that the most plausible approach for modelling TTD for selpercatinib was by assuming that TTD was equal to PFS, plus the observed time between progression and discontinuation in the populations of interest in LIBRETTO-001. For consistency between this submission and ID6132, which also models the any-line TC and MTC populations in LIBRETTO-001, assumptions for TTD in the base case economic analysis are unchanged in the model submitted alongside this response.

B 6. Section B.3.3.7 of the CS mentions that grade ≥3 adverse events with at least 2% difference in frequency between interventions were included in the model. However, Table 71 and Table 72 presents AEs with a smaller difference than 2% between selpercatinib and BSC. Please clarify the inconsistency and make sure the economic model is aligned with the report in case of discrepancy.

The model submitted alongside the CS included AEs where there was a ≥2% difference in frequency between any intervention featured in the model, which included some treatments which are not relevant to this submission.

As BSC is the only relevant comparator to selpercatinib in UK clinical practice for patients with *RET*-mutant MTC and *RET* fusion-positive TC who have received prior systemic therapy, Lilly have adjusted the model to only include AEs where there is a difference in frequency of ≥2% between selpercatinib and the placebo arm of the EXAM trial (for the *RET*-mutant MTC model) and the placebo arm of the SELECT trial (for the *RET* fusion-positive TC population). As demonstrated by the Figure 45 and Figure 46 of the CS, Document B, AEs have an extremely negligible impact on the ICER, therefore this change had a very minimal impact on the model results.

The results of the updated cost-effectiveness model are provided in Appendix A:

B 7. Section B.3.3.4 of the CS mentions in Table 74 and 75 the utility decrements for Grade 3 and 4 adverse events assuming the same decrement for all AE based on TA516. However, for the TC population a difference decrement value is used for diarrhoea and fatigue. Please clarify why diarrhoea and fatigue are different between the MTC and TC population.

Lilly would like to clarify that utility decrements for specific AEs were used in the model, where available. Where no specific utility decrement was identified, the estimate for any AE used In NICE TA516 (Assessment Group model) based on Beusterien *et al.* (2009)[27] was applied. As a result, a specific estimate was identified for diarrhoea and fatigue, from TA535[10] (Table 19, page 536 of the TA535 Draft Guidance Committee Papers). Therefore, the decrement of 0.38 for diarrhoea and of 0.08 for fatigue, as included in the model, are the correct values.

B 8. Please provide graphs similar to Figures 37-40, but with the (smoothed) hazard curves for all distributions explored

Stratified parametric and smoothed hazard curves, and unstratified parametric and smoothed hazard curves corresponding to Figures 37–40 in the CS have been produced by Lilly. For simplicity, these figures are provided within the reference pack submitted alongside this response document.[28]

Health-related quality-of-life data

B 9. **Priority. The EAG in TA742 requested the HRQoL data from the LIBRETTO-001 study to be mapped to EQ-5D values. In the current appraisal the updated EORTC-QLQ-C30 trial data from the any-line RET-altered TC and MTC populations (from 13th of January 2023 DCO) 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). It seems that the included mapping algorithms are solely those that the EAG identified in TA742. Please explain if any effort was made to identify more recent studies for the mapping algorithms through an SLR. If not, please provide such SLR. From a quick search the EAG was able to identify a mapping study by Huang et al. in Quality of Life research 2024 that was done in patients with papillary thyroid carcinoma, and a systematic review by Houten in Quality of Life research 2021 that might be of relevance.**

Lilly would like to thank the EAG for highlighting the additional mapping algorithms available for the purposes of mapping EORTC-QLQ-C30 data collected in the LIBRETTO-001 trial to EQ-5D data.

Following guidance from the NICE technical team in the ongoing appraisal for selpercatinib in the first-line thyroid indication (ID6132), however, Lilly have updated the base case cost-effectiveness analysis in this response to incorporate the utility values derived from EORTC-QLQ-C30 data from the any-line *RET* fusion-positive TC population, mapped to EQ-5D data using the Young, et al. 2015 algorithm.[21] These values have been adopted for consistency with this appraisal, which also utilises the any-line TC and MTC patient populations from the LIBRETTO-001 trial in its cost-effectiveness model. Adoption of these utilities reflects the appraisal committee's preferences for these values over the Fordham, et al. 2015 health state utility values used in the original base case for this submission.[16, 20]

The utility values used in the updated company base case (Appendix A:) provided alongside this response are presented in Table 73, Section B.3.4.2 of the CS, and are reproduced in Table 50 below.

Finally, Lilly would like to clarify that no additional searches were conducted to identify additional mapping algorithms.

Table 50: 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[a]		
Mapped to EQ-5D (Young 2015)[c]	[redacted]	[redacted]
LIBRETTO-001 EORTC data for *RET* fusion-positive TC[b]		
Mapped to EQ-5D (Young 2015)[d]	[redacted]	[redacted]

[a] *RET*-mutant MTC (any-line population). [b] *RET* fusion-positive 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: Lilly data on file, 2023,[7], Young *et al*. (2015),[21]

Costs and health care resource use

B 10. **Priority. In Section B.3.5.1 it is mentioned that the proportion of selpercatinib administrations at each dose level was informed from the recorded doses received in the LIBRETTO-001 trial (Table 79), adjusted to reflect the available tablet sizes (40 mg and 80 mg). It is also reported that adjustments in the dosing schedule were adjusted "such that the mean dose intensity matched that observed in the LIBRETTO-001 trial ([redacted]% for *RET*-mutant MTC SAS; [redacted]% for *RET* fusion-positive TC SAS)."**

a) Please explain where in the model the user can find the mean dose intensities mentioned above for the selpercatinib treatment.

The mean dose intensity can be found in the 'Country-Specific Data MTC' (row 115+) and 'Country-Specific Data TC' (row 100+) sheets of the model.

b) If the RDI percentage is not an individual input in the model, please explain how this RDI percentage has been reflected in the calculations. Please be detailed in your explanation. Please run a scenario analysis in which RDI for both populations is set at 100%.

The relative dose intensity (RDI) percentage for selpercatinib is not an individual input in the model. As noted in Section B.3.5.1 of the CS, the proportion of selpercatinib administrations at each dose level was based on the recorded doses received in the LIBRETTO-001 trial. Therefore, the proportion of patients receiving each dose of selpercatinib at each cycle was included in the model (as presented in Table 79, Section B.3.5.1 of the CS). These inputs were such that the mean dose intensity matched that observed in the LIBRETTO-001 trial ([redacted] for RET-mutant MTC SAS; [redacted] for RET fusion-positive TC SAS). This approach is in line with that accepted in TA742, and was also adopted in ID6132.[3] [16]

Given that the price of selpercatinib is scaled to reflect the dosage, such that dose reductions result in treatment cost reductions, a scenario analysis in which the RDI is set to 100% (i.e., removal of the RDI) would not be appropriate. Setting the RDI to 100% (i.e., removal of the RDI) would likely substantially overestimate drug acquisition costs for selpercatinib. The inclusion of a RDI multiplier in the model, to reflect dose reductions because of treatment toxicity, aligns with the preferences of the Committee in the ongoing appraisal for selpercatinib in untreated RET-altered TC and MTC (ID6132). The EAG in NICE ID6132 provided scenarios in which the RDI was removed (i.e., set to 100%); however, these analyses suggested that when RDI was removed, dose reductions did not result in treatment cost reductions. As selpercatinib has different prices for different doses, and as dose reductions would subsequently result in treatment cost reductions.

As a result, the Committee in NICE ID6132 concluded that an RDI multiplier should be included for selpercatinib.[16] Therefore, in this submission, Lilly have followed the guidance from the NICE technical team in the ongoing appraisal for selpercatinib in the first-line thyroid indication (ID6132), thus reflecting the appraisal committee's preferences, by including an RDI multiplier for selpercatinib,

B 11. **Priority. The types of resource use and frequency of use to estimate costs in the PF and PD health states of both populations were based on the TA516 (2018) Assessment Group model (consistent with NICE TA742), which in turn were based on previously obtained clinical expert opinion. Considering this appraisal was conducted in 2018, please provide additional evidence to justify that values for both types of resource and frequency are still valid for the current appraisal.**

As outlined in 0there are currently no other selective *RET* kinase inhibitors available in UK clinical practice.[1] Combined with the rarity of thyroid cancer, there have been a lack of therapeutic developments in this space since the publication of TA742. Due to this lack of development, there is no reason to suggest resource use in this population will have changed, as no novel therapies are available to necessitate these changes.[2, 3]

Furthermore, selpercatinib is an oral treatment that may therefore be associated with low resource use; the resource use incorporated into the cost-effectiveness model for each population are therefore likely conservative estimates.

B 12. Table 82 and Table 83 of the CS present the unit costs for AEs which are based on a 'non-elective inpatient setting'. However, the EAG in TA742 used the respective AE costs pertaining to a 'non-elective short stay' setting. Please explain if the EAG's concerns around this matter in TA742 have been resolved in the current appraisal and why the presented costs in the CS based on the 'non-elective inpatient setting' should be considered more suitable for this appraisal instead of the 'non-elective short stay' setting costs.

The EAG report for TA742 states that "As was also indicated by the company in response to the ERG's clarification questions, the Assessment Group in TA516 considered that the costs of a 'non-elective inpatient' setting may be more appropriate".[3] Accordingly, TA516 states that "the Assessment Group notes that all NHS Reference Cost codes assume that the patient is treated in an elective inpatient setting; given that these costs are associated with the management of AEs (i.e. non-elective), this is inappropriate but is likely to have only a negligible impact upon the model results". As such, the model for this submission incorporates non-elective AE costs in line with the Assessment Group's preferences in TA516.[9]

As shown by Figure 45, Section B.3.11.2 of the CS, the deterministic sensitivity analysis indicates that AE costs are not an influential factor on the ICER for selpercatinib versus BSC in either population. As such, the choice of AE reference costs used in the cost-effectiveness analysis are unlikely to have a large effect on the model results.

Section C: Textual clarification and additional points

C 1. In Table 52, which provides a list of published cost-effectiveness studies, TA535 (2018), UK, CUA is included twice (in rows 3 and 4 of the table), while describing different studies. Please confirm if that is a typographical error and indicate if one of the two rows should refer to TA928 which is not included in the table, while it is mentioned in the main text.

Lilly can confirm that rows 3 and 4 presented in Table 52, Section B.3.1 of the CS are correct. NICE TA535 was an appraisal of lenvatinib and sorafenib for treating DTC after radioactive iodine.[10] In NICE TA535 the model for lenvatinib included 4 health states (stable disease, response, progressive and death), whereas the model for sorafenib included only 3 health states (progression-free, progressed and death).[10] Therefore, in Table 52 of the CS, row 3 is allocated to the evaluation of the cost-effectiveness of lenvatinib, while row 4 is allocated to the evaluation of the cost-effectiveness of sorafenib, as appraised in TA535.

Appendix A: Revised base case cost-effectiveness analysis

Deterministic base case results

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. A summary of changes are provided below:

- Utility values for the progression-free and progressed health states in the *RET*-mutant MTC and *RET* fusion-positive TC population have been updated from the Fordham et al. 2015 vignette study values to data mapped from the LIBRETTO-001 trial, for consistency with committee preferences in ID6132[3, 20]
- Inclusion of only grade ≥3 adverse events with at least 2% difference in frequency between selpercatinib and BSC
- During the updates made to the cost-effectiveness model for this response a minor error was identified in the cost-effectiveness model submitted alongside the company submission. This error has been updated in the version of the cost-effectiveness model submitted alongside this clarification question response. Full details of the error and subsequent correction are provided below:
    - The formula in column N of the "TC S(t) (2)" was originally as follows, in the model submitted following clarification questions:
      "=IF(AND(hSO3=1,B10>='Survival - TC'!$D$60),IF(M11=0,0,-LN(M11)-(-LN(M10)))*'Survival - TC'!$D$62,IF(M11=0,0,-LN(M11)-(-LN(M10))))"
    - This has now been updated to:
    - "=IF(AND($O$3=1,B11>='Survival - TC'!$D$60),IF(M11=0,0,-LN(M11)-(-LN(M10)))*'Survival - TC'!$D$62,IF(M11=0,0,-LN(M11)-(-LN(M10))))"
    - This update ensures that the adjustment factor (relevant to selpercatinib OS) is applied from the correct timepoint in the model.

A summary of the updated deterministic base case analysis for RET-mutant MTC and RET fusion-positive TC is presented below.

RET-mutant MTC

A pairwise comparison for selpercatinib versus BSC has been conducted for the base case. A summary of the deterministic base case pairwise comparisons for selpercatinib (at PAS price) versus BSC in *RET*-mutant MTC are presented in Table 51 (at the updated selpercatinib PAS price).

The deterministic base case cost-effectiveness results (at selpercatinib PAS price) show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be [redacted] compared with [redacted] for patients treated with BSC (an incremental cost of [redacted]). The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with 1.91 for patients treated with BSC (an incremental QALY gain of [redacted]), resulting in an ICER of £39,976 per QALY gained versus BSC, including a 1.2x severity modifier.

The results presented include a confidential PAS discount for selpercatinib.

Table 51: Pairwise deterministic base-case results for selpercatinib versus BSC in *RET*-mutant MTC (at selpercatinib PAS price, with 1.2x severity modifier)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,976
BSC	16,557	2.67	1.91	-	-	-	-

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

RET fusion-positive TC

An overview of the pairwise deterministic base-case cost-effectiveness results for the *RET* fusion-positive TC population can be found in Table 52 (at selpercatinib PAS price).

The deterministic base case cost-effectiveness results (at selpercatinib PAS price) show that over a lifetime time horizon, the total costs associated with selpercatinib are estimated to be £[redacted], compared with £15,898 for patients treated with BSC (incremental costs are £[redacted]). The total QALYs for patients receiving selpercatinib and BSC are estimated to be [redacted] and 1.65, respectively (an incremental QALY gain of [redacted]). This results in an ICER for selpercatinib versus BSC of £36,306 per QALY gained, including a 1.2x severity modifier.

The results presented include a confidential PAS discount for selpercatinib.

Table 52: Pairwise deterministic base-case results for selpercatinib versus BSC for *RET* fusion-positive TC (at selpercatinib PAS price, with 1.2x severity modifier)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,306
BSC	15,898	2.31	1.65	-	-	-	-

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

References

1. Cancer Research UK. Thyroid cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer [Last accessed: 25th April 2023].
2. National Institute for Health and Care Excellence. TA928: Cabozantinib for previously treated advanced differentiated thyroid cancer unsuitable for or refractory to radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta928 [Last accessed: 16th January 2024].
3. National Institute for Health and Care Excellence. TA742: Selpercatinib for treating advanced thyroid cancer with RET alterations. Available from: https://www.nice.org.uk/guidance/ta742. [Last accessed: 25th April 2023].
4. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. [Last accessed: 30th April 2024].
5. NHS England. National Cancer Drugs Fund List. 10th May 2024. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/National-Cancer-Drugs-Fund-list-version-1.306.pdf. [Last accessed 15th May 2024].
6. American Cancer Society. Thyroid Cancer Survival Rates, by Type and Stage. Available from: https://www.cancer.org/cancer/types/thyroid-cancer/detection-diagnosis-staging/survival-rates.html. [Last accessed: 25th April 2023].
7. Eli Lilly Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).
8. Wirth LJ, Brose MS, Subbiah V, et al. Durability of Response With Selpercatinib in Patients With RET-Activated Thyroid Cancer: Long-Term Safety and Efficacy From LIBRETTO-001. Journal of Clinical Oncology 2024:JCO. 23.02503.
9. National Institute for Health and Care Excellence. TA516: Cabozantinib for treating medullary thyroid cancer. Available at: https://www.nice.org.uk/guidance/ta516 [Last accessed: 25th April 2023].
10. National Institute for Health and Care Excellence. TA535: Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta535 [Last accessed: 25th April 2023].
11. National Institute for Health and Care Excellence. TA550: Vandetanib for treating medullary thyroid cancer. Available at: https://www.nice.org.uk/guidance/ta550 [Last accessed: 25th April 2023].
12. Eli Lilly Data on File. LIBRETTO-001 Trial Protocol. 3rd June 2020.
13. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. New England Journal of Medicine 2015;372:621-630.
14. European Medicines Agency. Retsevmo. EPAR Product Information. Available from: https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_en.pdf. [Last Accessed: 20th March 2024].
15. Eli Lilly Data on File. Thyroid Cancer Clinical Expert Validation Interviews. Meeting Minutes. 2020.
16. National Institute for Health and Care Excellence. ID6132: Selpercatinib for untreated advanced thyroid cancer with RET alterations. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11047. [Last accessed: 14th February 2024].
17. Sherman SI, Clary DI, Elisei R, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer 2016;122:3856-3864.
18. Schlumberger M, Elisei R, Müller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Annals of Oncology 2017;28:2813-2819.
19. Latimer N. NICE DSU Technical Support Unit 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. [Last accessed: 16th May 2024].
20. Fordham BA, Kerr C, de Freitas HM, et al. Health state utility valuation in radioactive iodine-refractory differentiated thyroid cancer. Patient Prefer Adherence 2015;9:1561-72.
21. 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.

22. NHS England. 2018/19 National Cost Collection Data Publication. Available from: https://www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication/. [Last accessed 16th May 2024].
23. NHS England. 2021/22 National Cost Collection Data Publication. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication// [Last accessed: 8th May 2024].
24. Eli Lilly Data on File. Selpercatinib for untreated advanced RET altered TC and MTC Clinical Expert Validation Interviews. Meeting Minutes. 2023.
25. Raez LE, Kang H, Ohe Y, et al. Patient Reported Outcomes with Selpercatinib in Patients with RET driven cancers in the Phase 1/2 LIBRETTO-001 Trial. ESMO 2023:FPN 669P.
26. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. Journal of clinical oncology 2013;31:3639.
27. Beusterien K, Szabo S, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. British journal of cancer 2009;101:387-389.
28. Eli Lilly Data on File. Smoothed Hazard Curves for RET fusion-positive TC Survival Extrapolations. 2024.

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Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

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This form has 8 sections

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Section 1. About you

Table 1 Name, job, organisation

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] BTF [redacted] BTCT
4a. Provide a brief description of the organisation. 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 3,100 members and 2,700 supporters who we are regularly in touch with. 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/companies of the treatment and/or comparator products in the last 12 months? [Relevant	No – both organisations

companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of 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 helpline 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. Both charities 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.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	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.
7. What do carers experience when caring for someone with the condition?	
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	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.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	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.'*

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	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 reducing the dose he feels that the side effects he has had have been straightforward for him to deal with.

13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	

15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	No
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The patients who might benefit from this treatment are a very small, precisely targeted cohort and evidence suggests they this medicine offers the chance of 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.

Thank you for your time.

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Erasmus School of Health Policy & Management

Maastricht University

Selpercatinib for treating advanced thyroid cancer with *RET* alterations (MA review of TA742) [ID6288]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors

Marie Westwood, Reviews Manager, KSR Ltd, United Kingdom (UK)
Venetia Qendri, Research Associate HTA, Erasmus School of Health Policy & Management (ESHPM), EUR, Rotterdam EUR, the Netherlands (NL)
Mehlika Toy, Lecturer Health Technology Assessment (HTA), ESHPM, EUR, NL
Eline Krijkamp, Lecturer HTA, ESHPM, EUR, NL
Jiongyu Chen, Health Economist and Systematic Reviewer, KSR Ltd, UK
Caro Noake, Senior Information Specialist, KSR Ltd, UK
Maiwenn Al, Senior Lecturer HTA, ESHPM, EUR, NL
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK

Correspondence to

Kleijnen Systematic Reviews Ltd
FAO Marie Westwood
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

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*[redacted]

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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.

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Contributions of authors:

Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Venetia Qendri, Mehlika Toy and Eline Krijkamp acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Jiongyu Chen acted a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Nigel Armstrong acted as health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and the company's economic evaluation, contributed to the writing of the report and provided general guidance. Marie Westwood and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AACR	American Association for Cancer Research
ACP	American College of Physicians
ACTH	Adrenocorticotropic hormone
AE	Adverse events
AESI	Adverse events of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the curve
BIC	Bayesian information criterion
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
Cab	Cabozantinib
CADTH	Canadian Agency for Drugs and Technologies in Health
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Carcinoembryonic antigen
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
cfDNA	Circulating free DNA
CI	Confidence interval
Cmax	maximum drug concentration
CNS	Central nervous system
CON	Confidential
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DARE	Database of Abstracts of Reviews of Effect
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DTC	Differentiated thyroid cancer
EAG	Evidence Assessment Group
EBM	Evidence-Based Medicine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions

ESMO	European Society of Medical Oncology
EUR	Erasmus University Rotterdam
FISH	Fluorescence in situ hybridisation
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICTRP	International Clinical Trials Registry Platform
iDBC	Institute for Medical Technology Assessment Disease Burden Calculator
IRC	Independent review committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews Ltd
LPS	Lansky Performance Score
LTFU	Long-term follow-up
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MKI	Multikinase inhibitor
MTC	Medullary thyroid cancer
MTC:Cab/Van	Prior cabozantinib/vandetanib *RET*-mutant MTC population
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NE	Not estimable
NGS	Next generation sequencing
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
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	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PPI	Proton pump inhibitor
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSW	Propensity score weighting

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
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
RET	Rearranged during transfection
RP2D	Recommended Phase II dose
RPSFT	Rank preserving structure failure time
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
SD	Standard deviation
SFU	Safety follow-up
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
SRC	Safety Review Committee
STA	Single Technology Appraisal
TA	Technology Assessment
TC	Thyroid cancer
TC:TrtSys	Prior systemic therapy *RET* fusion-positive TC population
TE	Treatment emergent
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
Tmax	Time to maximum plasma concentration
TSD	Technical support document
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC+	University Medical Centre+
Van	Vandetanib
VEGF/VEGFR	Vascular endothelial growth factor/vascular endothelial growth factor receptor
WHO	World Health Organization

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1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 is related to the clinical effectiveness, and Section 1.5 is related to the cost effectiveness. A summary in presented in Section 1.6.

Further information on the technology and evidence, and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness), and 4 and 5 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

#	Summary of issue	Report Sections
1	Lack of direct evidence about the efficacy and safety of selpercatinib versus best supportive care	3.2 to 3.4
2	Lack of consideration of alternative sources of data for ITCs	3.1, 3.3
3	Population mismatch	3.2.5, 4.2.3
4	Selecting best extrapolation of survival data	4.2.6, 6.2 and 6.3
ITC = indirect treatment comparisons		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased progression-free survival and overall survival
- Disutilities due to treatment-related adverse events.

Overall, the technology is modelled to affect costs by:

- Its additional drug acquisition costs (i.e. a higher unit price than current treatment), pharmacy dispensing costs, monitoring costs, and costs for the treatment of adverse events.
- The need for genetic testing to assess eligibility for treatment.

The modelling assumptions that have the greatest effect on the ICER are:

- Use of extrapolations for progression-free and overall survival based on alternative parametric functions.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is in line with the final scope issued by NICE.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.2: Key issue 1: Lack of direct evidence about the efficacy and safety of selpercatinib versus best supportive care

Report Section	3.2 to 3.4
Description of issue and why the EAG has identified it as important	There is a lack of direct evidence about the comparative efficacy and safety selpercatinib versus BSC, in the specified populations. There is also a lack of trials comparing either the intervention or BSC to a common comparator. This has necessitated the use of ITCs, using single arm data, to generate estimates of treatment effect and to inform cost-effectiveness modelling.
What alternative approach has the EAG suggested?	The EAG acknowledges that there are no planned or ongoing RCTs of selpercatinib, in the specified populations, and that this is unlikely to change. The EAG, therefore, made a number of requests (in clarification questions to the company) which aimed to ensure that all potential options to reduce the high level of uncertainty around the results comparing selpercatinib indirectly with BSC (noted in TA742). These requests are described in key issue 2.
What is the expected effect on the cost effectiveness estimates?	The expected change to the point estimate of the ICER is unclear. However, the uncertainty surrounding the ICER estimates is increased by this issue.
What additional evidence or analyses might help to resolve this key issue?	Given that this is a managed access agreement review, it is very disappointing that there appear to be almost no new data to help to resolve the uncertainty in relation to lack of comparative evidence identified in TA742.
BSC = best supportive care; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; RCT = randomised controlled trial; TA = technology appraisal	

Table 1.3: Key issue 2: Lack of consideration of alternative sources of data for ITCs

Report Section	3.1, 3.3
Description of issue and why the EAG has identified it as important	For *RET*-mutant MTC, the EXAM trial was chosen instead of the ZETA trial and of *RET* fusion thyroid cancer the SELECT trial instead of DECISION. On balance, the EAG does agree that those chosen were probably the more appropriate of the two sets of trials considered. However, because only an unanchored ITC (single arms only) was feasible, it is unclear why the company only conducted searches for all study designs for the *RET*-altered TC and MTC populations. For the wider TC and MTC populations, only RCTs were considered as the source of comparator data. The EAG also had serious concerns about the searches used to retrieve studies for the systematic review and considers that the application of different study design criteria to the *RET*-altered and the wider TC and MTC populations was not appropriate. It was also the conclusion of the Committee in TA742 that, based on the same data source, the results of the MAIC were uncertain because of

Report Section	3.1, 3.3
	limitations of the EXAM trial as a comparator data source in this population.
What alternative approach has the EAG suggested?	The company were asked in the clarification letter to conduct a systematic review designed to retrieve all potential sources of evidence for an ITC with BSC in both populations. However, this was not performed.
What is the expected effect on the cost effectiveness estimates?	The expected change to the point estimate of the ICER is unclear. However, the uncertainty surrounding the ICER estimates is increased by this issue.
What additional evidence or analyses might help to resolve this key issue?	The company should conduct a systematic review to search for and summarise all potential sources of data to inform the effectiveness of treatment with BSC. These sources should include single arms from trials and observational data. Any additional data that is retrieved in this new systematic review should then be compared to the EXAM and SELECT trials and the feasibility of use in additional ITCs assessed.
BSC = best supportive care; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; MTC =medullary thyroid cancer; RCT = randomised controlled trial; *RET* =rearranged during transfection	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The EAG's summary and detailed critique can be found in Section 4, the company's cost effectiveness results are presented in Section 5, and the EAG's amendments to the company's model and results are in Section 6. The key issues in the cost effectiveness evidence are discussed below.

Table 1.4: Key issue 3: Population mismatch

Report Section	3.2.5, 4.2.3
Description of issue and why the EAG has identified it as important	The company used survival data for a mixed population (consisting of naïve and previously treated patients) for both selpercatinib and BSC arms which is inconsistent with the population that is relevant for the decision problem of this appraisal, i.e. only previously treated patients. As a result, any ICER that follows from this comparison is unlikely to be an unbiased estimate of the true cost effectiveness in second line.
What alternative approach has the EAG suggested?	The company justifies the mixed population analyses by referring to the fact that in the SELECT and EXAM trials results were not reported stratified by naïve and previously treated. The EAG asked the company to reproduce the survival analyses by removing the patients with RET-mutant MTC who were naïve to cabozantinib and/or vandetanib and patients with RET fusion-positive TC that were naïve to prior lenvatinib and/or sorafenib and include these results in the scenario analyses. The company declined to conduct such analyses arguing that this would be expected to substantially bias results against selpercatinib. Whilst the EAG concurs with that expectation, the requested scenario

Report Section	3.2.5, 4.2.3
	could serve as a lower limit, thus providing relevant information for decision making.
What is the expected effect on the cost effectiveness estimates?	The ICERS would most likely be higher, as it is to be expected that OS of the previously treated population ≤ OS of the mixed population ≤ OS of the naïve population. These ICERs could be regarded as an upper limit of the potential influence of the population.
What additional evidence or analyses might help to resolve this key issue?	The impact of the population mismatch may be explored by only including treatment experienced patients with RET-mutant MTC or RET fusion-positive TC in the estimation of comparative effectiveness for the cost effectiveness analyses. As the EXAM and SELECT trial do not stratify results according to previous treatments, such scenarios would provide an upper limit for the ICERs. If, as suggested for key issue 2, alternative sources to estimate BSC PFS and OS are found, these might include data specific for treatment experienced patients.
BSC = best supportive care; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MTC = medullary thyroid cancer; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection; TC = thyroid cancer	

Table 1.5: Key issue 4: Selecting best extrapolation of survival data

Report Section	4.2.6, 6.2, and 6.3
Description of issue and why the EAG has identified it as important	The OS and PFS data were extrapolated using parametric survival curves. In both populations, due to the immature data, many curves provided a reasonable fit to the observed data, whilst showing large variation for the extrapolated part. In that regard, the EAG understands the company's prioritisation of clinical plausibility for the selection of the survival models over the goodness-of-fit measures and visual inspection. The clinical plausibility is currently assessed using expert opinion on 10- and 20-year PFS and OS probabilities, as provided for the appraisal for selpercatinib in untreated patients (ID6132). Two problems arise here: 1) PFS and OS are expected to be lower for selpercatinib arm and likely also the BSC arm, so the estimates provided by experts in ID6132 are of limited value. 2) whilst experts are likely to have enough experience with patients receiving BSC to provide reasonable 10- and 20-year survival estimates, such experience does not exist for patients receiving selpercatinib, making the long-term survival estimates in this group rather speculative.
What alternative approach has the EAG suggested?	A small improvement could be made by asking clinical experts to reflect more specifically of survival for treatment experienced patients, and by also asking for estimates of the 5-year survival probabilities. The latter would allow for more data points to

Report Section	4.2.6, 6.2, and 6.3
	which parametric curves can be compared, plus the experts would likely be more certain about estimating 5-year survival versus 20-year survival.
What is the expected effect on the cost effectiveness estimates?	The results of the ERG scenarios in section 6.3 of this report show the range of potentially plausible ICERs obtained from changing either PFS or OS in each population. These results show that the range of potentially plausible ICERs ranges from £39,370 to £57,185 (£32,808 to £47,654 after severity weighting) for the RET-mutant MTC population and £38,836 to £54,333 (£32,363 to £45,278 after severity weighting) for the RET-fusion positive TC population. These ranges are based on the assumption that the underlying data is representative of the population who will receive selpercatinib in clinical practice, and the unbiased estimation of relative treatment efficacy with the MAIC and naïve ITC.
What additional evidence or analyses might help to resolve this key issue?	Mature survival data from a head-to-head trial matching the population who will receive selpercatinib in clinical practice would be required to resolve the uncertainty fully. However, for the issue of extrapolation of the OS curves, the most important element is maturity of the survival data; as this improves, the variability between the various modelled curves will decrease.
BSC = best supportive care; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MTC = medullary thyroid cancer; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection; TC = thyroid cancer	

1.6 Summary of the EAG's view

The EAG preferred assumptions are described in detail in section 6.1 of this report and the resulting ICERS are summarised in Tables 1.6 and 1.7, in comparison to the company original base-case and the company base-case following clarification. See Section 6.3 for exploratory and sensitivity analyses carried out by the EAG.

Table 1.6: Summary of EAG's preferred assumptions and ICER, RET-mutant MTC, (selpercatinib PAS price, discounted)

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
CS original base-case					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	47,681
BSC	17,085	1.51	-		
CS base-case following the clarification phase					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	48,078 (40,065)
BSC	16,562	1.91			

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
EAG base-case: individual impact of using gamma distribution to model PFS					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	44,476 (37,063)
BSC	16,562	1.90	-		

Based on the electronic model following the clarification phase.[1, 2]
*Values in the parenthesis account for a QALY weight of 1.2 in both populations.
BSC = best supportive care; CS = company submission; EAG = external assessment group; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; PAS = patient access scheme; PFS = progression-free survival; RET = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer

Table 1.7: Summary of EAG's preferred assumptions and ICER, RET fusion-positive TC, (selpercatinib PAS price, discounted)

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
CS original base-case					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	45,047
BSC	16,030	1.27	-		
CS base-case following the clarification phase					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	43,567 (36,306)
BSC	15,898	1.65	-		
EAG base-case: individual impact of using the stratified gamma distribution to model OS					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	46,699 (38,916)
BSC	15,452	1.47			

Based on the electronic model following the clarification phase.[1, 2]
*Values in the parenthesis account for a QALY weight of 1.2 in both populations.
BSC = best supportive care; CS = company submission; EAG = external assessment group; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; OS = overall survival; PAS = patient access scheme; RET = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer

2. Critique of company's definition of decision problem

The decision problem defined in the final National Institute for Health and Care Excellence (NICE) scope[3] reflects the recommendation of selpercatinib for use within the Cancer Drugs Fund (CDF) following TA742:[4]

- For advanced rearranged during transfection (*RET)*-mutant medullary thyroid cancer (MTC) in people aged 12 years and older who require systemic therapy after cabozantinib or vandetanib
- For advanced *RET* fusion-positive thyroid cancer (TC) in people aged 12 years and older who require systemic therapy after sorafenib or lenvatinib.

The company submission (CS)[5] notes that both of the specified populations of interest are narrower than the anticipated full marketing authorisation for selpercatinib:

- As monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant MTC
- As monotherapy for the treatment of adults and adolescents 12 years and older with advanced *RET* fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate).

The CS also notes that: *'The remaining populations within the licensed indications (i.e., patients who have not previously received systemic therapy) are currently undergoing appraisal as part of the ongoing submission for selpercatinib in untreated RET-altered TC and MTC (ID6132).'*[5]

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with advanced *RET* fusion-positive thyroid cancer who require systemic therapy after sorafenib or lenvatinib People with advanced *RET* mutation-positive MTC who require systemic therapy after cabozantinib or vandetanib	Adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib or sorafenib* Adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib or vandetanib*	NA – in line with the NICE final scope	The EAG notes that the original wording in the CS included advanced *RET* fusion-positive TC, patients who have previously received treatment with both lenvatinib and sorafenib and, advanced *RET*-mutant MTC, patients who have previously received treatment with both cabozantinib and vandetanib. In their response to clarification questions, the company confirmed that the population addressed in the decision problem should not include these patients and requested that this table be amended accordingly. With respect to the LIBRETTO-001 study, the company also provided subgroup data for those patients in the *RET* fusion-positive TC prior treatment group who had received lenvatinib or sorafenib (i.e., excluding those patients who had received both drugs) and for patients in *RET*-mutant MTC prior treatment group who had received cabozantinib or vandetanib (i.e., excluding those

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				patients who had received both drugs). The EAG further notes that, for the advanced *RET* fusion-positive thyroid cancer who require systemic therapy after sorafenib or lenvatinib group, the population presented in the CS was: *"prior systemic therapy RET fusion-positive TC,"* 35/41 (85.4%) patients in this population had received a prior treatment regimen (sorafenib or lenvatinib) specified in the NICE scope.
Intervention	Selpercatinib	Selpercatinib	NA – in line with the NICE final scope.	The intervention is in line with the NICE scope.
Comparator(s)	For advanced *RET* fusion-positive thyroid cancer which has progressed following prior treatment: BSC or palliative care. For advanced *RET* mutation-positive MTC which has progressed following prior treatment: BSC or palliative care.	For advanced *RET* fusion-positive thyroid cancer which has progressed following prior treatment: BSC [redacted]For advanced *RET* mutation-positive MTC which has progressed following prior treatment: BSC	NA – in line with the NICE final scope.	The comparators are in line with the NICE scope.
Outcomes	The outcome measures to be considered include: • OS • PFS	The following outcomes have been included within the CS: • BOR and ORR	NA – in line with the NICE final scope.	The outcomes reported are in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Response rate • AEs of treatment • HRQoL	• DOR • Time to response and time to best response • CBR • OS • PFS • AEs of treatment • 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 economic analysis has been provided in line with the NICE reference case **Outcomes**: The incremental cost-effectiveness ratio (ICER) of selpercatinib versus each comparator was evaluated in terms of an incremental cost per QALY gained **Model time horizon**: 35 years in base-case **Model perspective**: The analysis was conducted from the perspective of the NHS and Personal Social Services **Commercial arrangements**: A confidential Patient Access	NA – in line with the NICE final scope.	According to NICE reference case and in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• The use of selpercatinib is conditional on the presence of *RET* mutation or fusion. The economic modelling should include the costs associated with diagnostic testing for *RET* mutation/fusion in people with advanced MTC/advanced thyroid cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	Scheme (PAS) 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.		
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • Type of thyroid cancer within advanced *RET* fusion-positive thyroid cancer (such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma). • Specific type of *RET* alteration (within *RET* fusion-positive thyroid cancer or *RET*-mutation positive MTC) may need to be considered, as some types of *RET* genetic alteration may be more or less sensitive to selpercatinib.	The following clinical efficacy subgroup analyses have been presented in the submission: ***RET* fusion-positive TC** • *RET* fusion type (objective response rate [ORR] and duration of response [DOR]) • Type of follicular TC (ORR only) ***RET*-mutant MTC** • *RET* mutation type (ORR and DOR)	It should be noted that although subgroup analyses are presented for these subgroups, results are limited by small patient numbers, particularly for the *RET* fusion-positive TC population (Section B.2.7 of the CS). Due to particularly small patient numbers by type of follicular TC and type of *RET*-mutation, no subgroup analyses were considered in the cost-effectiveness evaluation.	The EAG requested, at clarification, that the company provide data for all listed subgroups and for all outcomes available. The EAG also requested that these data be provided for the any-line populations, from LIBRETTO-001, used in the cost-effectiveness evaluation.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		No subgroup analyses were considered in the cost-effectiveness evaluation.		
Special considerations including issues related to equity or equality	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.	NA – in line with the NICE final scope.

Based on Table 1 in the CS[5]

*Amended following response to clarification[1]

AEs = averse events; BOR = best overall response; BSC = best supportive care; CBR = clinical benefit rate; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; MTC = medullary thyroid carcinoma; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ORR = objective response rate; OS = overall survival; PAS = Patient Access Scheme; PFS = progression-free survival; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer

2.1 Population

The population defined in the NICE final scope is:[3]

- People with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib
- People with advanced *RET* mutation-positive MTC who require systemic therapy after cabozantinib or vandetanib.

The decision problem addressed by the CS is restricted, for both of the above populations, to adults and adolescents aged 12 years and older; this is in-line with the full marketing authorisation for selpercatinib *"as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET-mutant MTC,"*[6] and with the anticipated marketing authorisation for selpercatinib *"as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate)."*[7]

The treatment pathway and proposed positioning of selpercatinib in patients with advanced *RET* fusion-positive TC, reported in the CS and illustrated in Figure 2.1,[5] appears to indicate that selpercatinib is currently available for patients with undifferentiated TC as an alternative to full thyroidectomy; it is the understanding of the Evidence Assessment Group (EAG) that TA742 recommended selpercatinib only after sorafenib or lenvatinib, which are given to patients with differentiated disease.

The decision problem addressed in the CS also differs from that specified in the NICE final scope in that it includes:

- People with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib ***and/or*** vandetanib
- People with advanced *RET* fusion-positive TC who require systemic therapy following prior treatment with lenvatinib ***and/or*** sorafenib

The CS also includes clinical effectiveness data for selpercatinib in the any-line *RET*-altered TC and MTC populations; data for these populations are used in the indirect treatment comparisons (ITCs) presented in the CS and in the cost-effectiveness analyses.[5]

EAG comment: The National Health Service (NHS) England CDF list specifies the following criteria: *"Either the patient has differentiated thyroid cancer (papillary/follicular/Hurtle cell) and has therefore been treated with lenvatinib or sorafenib or the patient has anaplastic thyroid cancer in which case no previous TKI treatment requirement is necessary."*[8] The EAG also notes that the LIBRETTO-001 trial included 4 patients with anaplastic thyroid cancer (ATC). The EAG requested clarification on whether or not the decision problem for this appraisal includes patients with undifferentiated/anaplastic TC. The company confirmed that: *"Since this CDF exit submission is a reassessment of TA742, patients with RET fusion-positive ATC should be included in the decision problem for this appraisal, in alignment with the patient populations considered in the original submission (TA742) and currently eligible to receive selpercatinib via the CDF."*[1] The company further clarified that for patients with undifferentiated TC, selpercatinib would be received after surgery, if required.

The EAG notes that the LIBRETTO-001 trial included [redacted] patients ([redacted]% of the prior cabozantinib/vandetanib *RET*-mutant MTC patient population) who had previously received both cabozantinib and vandetanib, and 4 patients (9.8% of the prior systemic therapy *RET* fusion-positive TC population) who had previously received both lenvatinib and sorafenib. The EAG requested

clarification on whether, in clinical practice, those with advanced *RET* fusion-positive TC who had only received only one of sorafenib or lenvatinib would then be eligible to receive the other, and those with advanced *RET* mutation-positive MTC who had received only one of cabozantinib or vandetanib would be eligible to receive the other; this has potential implications for relevant comparators (see Section 2.3). The company responded that: *"Lilly request that the population wording provided in Table 1 of the CS is updated to:*

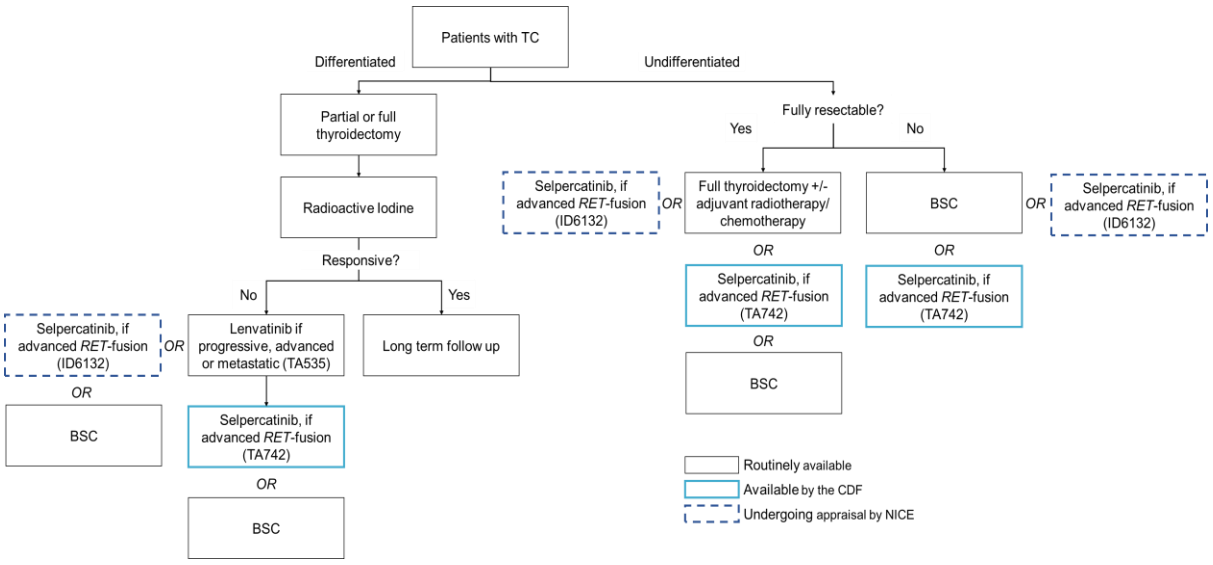
- *Adults and adolescents 12 years and older with advanced RET-mutant MTC who require systemic therapy following prior treatment with cabozantinib* ***or*** *vandetanib*
- *Adults and adolescents aged 12 years and older with advanced RET fusion-positive TC who require systemic therapy following prior treatment with lenvatinib* ***or*** *sorafenib"* (p. 16)

They further clarified that sequential treatment with multikinase inhibitors (MKIs) is not recommended in the United Kingdom (UK); this is consistent with clinical expert opinion on current UK practice, obtained by the EAG (Appendix 1).

The EAG notes that not all patients in the prior systemic therapy *RET* fusion-positive TC population from LIBRETTO-001, included in the CS, had received prior treatment with one of the two treatments specified in the NICE scope; 35/41 (85.4%) patients in this group had received prior treatment with sorafenib or lenvatinib.

The EAG requested provision of subgroup analyses, for participants in the LIBRETTO-001 study in the *RET* fusion-positive TC prior treatment group who had received lenvatinib or sorafenib (i.e., excluding those patients who had received both drugs) and those in *RET*-mutant MTC prior treatment group who had received cabozantinib or vandetanib (i.e., excluding those patients who had received both drugs). These data were provided and are included in Section 3.2.5 of this report.[1]

Figure 2.1: Treatment pathway and proposed positioning of selpercatinib in patients with advanced *RET* fusion-positive thyroid cancer



Based on Figure 5 in the CS[5]
BSC = best supportive care; CDF = Cancer Drugs Fund; CS = company submission; NICE = National Institute for Health and Care Excellence; *RET* = rearranged during transfection; TA = technology appraisal; TC = thyroid cancer

2.2 Intervention

The NICE final scope specifies the intervention as selpercatinib.[3] The CS (Table 2, Section B.1.2) states that the recommended dose of selpercatinib, based on weight, is:[5, 6]

- Less than 50 kg: 120 mg orally, twice daily
- 50 kg or greater: 160 mg orally, twice daily.

All data on the clinical effectiveness of selpercatinib, included in the CS (Section B.2), were derived from the LIBRETTO-001 trial. It appears that all patients included in the LIBRETTO-001 trial received selpercatinib 160 mg orally, twice daily. In addition, the baseline characteristics provided for patients included in the LIBRETTO-001 trial (CS Tables 7 and 9) indicated that some patients whose body weight was less than 50 kg were included in the trial.

EAG comment: The EAG requested clarification on whether or not weight-based dosing was used in LIBRETTO-001 and on the numbers of participants in LIBRETTO-001 whose baseline body weight was less than 50 kg. The company confirmed that dosing in the LIBRETTO-001 trial was not based on body weight and provided additional information on the numbers of participants in the LIBRETTO-001 study whose baseline body weight was less than 50 kg (Table 2.2).[1]

Table 2.2: Participants in LIBRETTO-001 whose baseline body weight was less than 50 kg

Subgroup	Body weight at baseline <50 kg (n, %)
RET-mutant MTC prior cabozantinib/vandetanib N=152	[redacted]
RET-mutant MTC any-line population N=295	[redacted]
RET fusion-positive TC prior systemic therapy N=41	[redacted]
RET fusion-positive TC any-line population N=65	[redacted]
Based on response to clarification questions, Tables 41 and 42[1] MTC = medullary thyroid cancer; n = number of patients per category; N = number of patients in the population; *RET* = rearranged during transfection; TC = thyroid cancer	

2.3 Comparators

The NICE final scope specifies the comparator as best supportive care (BSC) or palliative care, for both of the specified populations.[3] The CS defines the comparator as BSC.[5] No specification for BSC or palliative care is provided in either the NICE scope or the CS.

EAG comment: The EAG notes that the CS does not include any direct evidence about the comparative efficacy of selpercatinib versus BSC, palliative care, or any other comparator. The ITCs, included in the CS (Section B.2.9) and critiqued in Section 3.4 of this report, used the placebo arms of two randomised controlled trials (RCTs), EXAM[9] for patients with advanced *RET*-mutant MTC and SELECT[10] for patients with advanced *RET* fusion-positive TC, as surrogates for BSC.[5] No details were reported regarding supportive/palliative care received by patients in the placebo arms of either of these two RCTs. The EAG therefore considers that it is unclear to what extent the placebo arms of the EXAM and SELECT trials represent a reasonable surrogate for BSC, as received by patients with advanced *RET*-mutant MTC and advanced *RET* fusion-positive TC, respectively, in the UK.

The EAG notes that if (as discussed in Section 2.1), in clinical practice, patients with advanced *RET* fusion-positive TC who had only received only one of sorafenib or lenvatinib would then be eligible to receive the other, and those with advanced *RET* mutation-positive MTC who had received only one of cabozantinib or vandetanib would be eligible to receive the other, then the other tyrosine kinase inhibitor (TKI) (as specified for each group) should be included as a comparator in both the clinical and cost effectiveness analyses. The EAG sought clarification regarding this to which the company responded as described in Section 2.1 i.e., sequential treatment is not recommended in the UK, thus ruling out any active treatment as comparator.[1]

2.4 Outcomes

The LIBRETTO-001 trial and the CS included data for all outcomes listed in the NICE scope. Health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30).[5] Data were also reported for the following additional outcome, not listed in the NICE scope:

- Duration of response (DOR)
- Time to response and time to best response
- Clinical benefit rate (CBR)

2.5 Other relevant factors

The CS notes that: *"Females are more likely to be diagnosed with thyroid cancer than males, with UK data indicating that 72% of thyroid cancer cases occur in females and the remaining 28% in males."* The company, therefore, argues that: *"Routine access to selpercatinib for the treatment of thyroid cancer in patients who have received prior systemic therapy will continue to reduce the health inequalities for female patients with thyroid cancer."*[5]

With respect to *RET* testing, the CS states: *"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."*[5]

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The CS reports that: *"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, ongoing 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."*[5]

Full details of the systematic literature review (SLR), including the search strategies, study selection process and detailed results were presented in Appendix D.[11]

EAG comment: The EAG considers that there are significant problems with the design of the systematic review presented in Appendix D of the CS. The comparator specified in the NICE scope and decision problem (Table 2.1), for both *RET*-mutant MTC and *RET*-fusion positive TC, is BSC or palliative care. The CS (Section B.2.9) uses ITCs, with data from the placebo arms of RCTs (as a proxy for BSC), to generate estimates of the comparative efficacy of selpercatinib. In order to ensure that all potential sources of comparator data have been considered, searches should be designed to identify any study with a placebo or BSC arm, which has been conducted in one of the specified populations, irrespective of the active intervention.

In their response to clarification questions, the company provided the following statement concerning the design of their SLR/search strategies:

"Lilly have not conducted new literature searches within the timeframe of the clarification questions, and maintain that the searches used in the clinical systematic literature review (SLR) informing this submission were sufficiently robust.

It is important to clarify that the current search strategies already included all studies including patients with rearranged during transfection (RET)-altered thyroid cancer, regardless of intervention, meaning that no studies in patients with RET-altered thyroid cancer for placebo/best supportive care (BSC) were missed.

Therefore, theoretically, the only studies for placebo/BSC that would not have been captured in the current searches are single-arm studies or randomised controlled trials (RCTs) including a placebo/BSC arm that did not explicitly include patients with RET-altered thyroid cancer. It is considered unlikely that any single-arm studies would have been conducted including patients receiving placebo/BSC, given the ethical concerns that would be associated with such a study.

Therefore, it is only necessary to consider if any RCTs including placebo/BSC arms have been excluded from the SLRs. The searches included a comprehensive range of potentially used treatments for thyroid cancer, including selpercatinib, pralsetinib, cabozantinib and vandetanib (for medullary thyroid cancer [MTC]) and selpercatinib, pralsetinib, lenvatinib and sorafenib (for thyroid cancer [TC]). Therefore, the only studies which might have been omitted would be RCTs for alternative treatments that additionally included a placebo arm. However, as the searches already included all treatments recommended by NICE for the treatment of either TC and MTC, as well as additional treatments, such

as pralsetinib, then it is considered that the current search strategy is extremely unlikely to have omitted any evidence that would be more relevant than the SELECT and EXAM trials used to inform the efficacy of BSC in the MTC and TC populations, respectively, given the paucity of other treatment options for patients with thyroid cancer."

The EAG acknowledges that the documented approach aimed to identify RCTs of *"all treatments recommended by NICE for the treatment of either TC and MTC, as well as additional treatments,"* but maintains that this approach is not adequate to objectively demonstrate that there are not more relevant sources of comparator data than the SELECT and EXAM trials.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[12] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the SLR conducted to identify relevant clinical evidence on efficacy and safety of selpercatinib and BSC for advanced or metastatic *RET*-altered MTC and TC.[11] The original searches were conducted in September 2019, with subsequent updates in October 2020, July 2021, September 2022 and May 2023. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the original 2019 clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date of last search
Electronic databases		
Embase	Elsevier	25.9.19
MEDLINE ALL and MEDLINE In-Process	PubMed	25.9.19
CDSR	Cochrane Library (Wiley)	25.9.19
CENTRAL	Cochrane Library (Wiley)	25.9.19
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission		

EAG comment:

- The original searches were undertaken in September 2019 to identify clinical evidence on efficacy and safety of selpercatinib and BSC for advanced or metastatic *RET*-altered MTC and TC. These searches were critiqued in the 2020 EAG report. The EAG report concluded that whilst a good range of databases and additional resources were searched, the original searches could have benefited from better use of database search tools, a more sensitive population facet for the clinical efficacy searches and additional searches for safety evidence. As no changes were made to these searches please see the 2020 report for the full search critique.[13]

Table 3.2: Data sources for the clinical effectiveness systematic review update searches (as reported in CS)

Resource	Host/Source	Date Ranges	Date of last search
Electronic databases			
Embase	Ovid	2019-2023/05/24	24.5.23
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	2019-2023/05/24	24.5.23
EBM reviews (all elements including Cochrane CDSR & CENTRAL, DARE, NHS EED and ACP Journal Club)	Ovid	2019-2023/05/24	24.5.23
Conferences			
• ASCO • ESMO • ESMO Immuno-Oncology Congress • AACR • European Congress of Endocrinology • American Head and Neck Conference • ATA • World Congress on Thyroid Cancer • European Thyroid cancer	Internet	2019-2023 (where appropriate)	Not reported
Trials registries			
• www.ClinicalTrials.gov • WHO ICTRP	Internet	Inception-2023/05/24	24.5.23

AACR = American Association for Cancer Research; ACP = American College of Physicians; ASCO = American Society of Clinical Oncology; ATA = American Thyroid Association; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EBM = Evidence-Based Medicine; ESMO = European Society of Medical Oncology; NHS EED = National Health Service Economic Evaluation Database; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform

- The strategies reported as update searches utilised different search strategies and were carried out on different host interfaces. These searches were conducted in October 2020, July 2021, September 2022 and May 2023 and are critiqued here. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.
- A good range of bibliographic databases, conferences and trials registers were searched. However, the EAG found the searches to be both overcomplicated and restrictive.

Table 3.3: CS SLR search algorithms[1]

Search algorithm	Single-arm trials or RCTs in *RET* tumours (any tumour type, all interventions, any LOT
Line item 1	MTC AND RET AND STUDY DESIGN (REGARDLESS OF TX - RET) – string 18
Line item 2	PTC/DTC AND RET AND STUDY DESIGN (REGARDLESS OF TX - RET) – string 20
Search algorithm	RCTs in MTC/PTC/DTC (any LOT)
Line item 3	MTC AND INTERVENTION AND RCT DESIGN (WITH TX – NO RET) – string 22

Line item 4	PTC/DTC AND INTERVENTION AND RCT DESIGN (WITH TX – NO RET) – string 24
CS = company submission; DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; PTC = papillary thyroid cancer; RCT = randomised controlled trial; *RET* = rearrangements and/or mutations during transfection; SLR = systematic literature review	

- The condition facet which contained relevant subject headings not included in the final line combinations (see point below) was of particular concern. The EAG suggested that a more appropriate approach would have been to search for terms for thyroid cancer combined with a facet for *RET* mutations. The company declined to rerun the searches stating that they believed the existing searches to be suitably robust. Furthermore, they stated that the suggested approach which focuses on *RET*-altered patients only, as per the NICE Scope, would have missed papers such as the SELECT Trial. Whilst the EAG accepts the company's decision to search beyond *RET*-altered patients, the EAG does not agree that the searches were suitably robust and remains concerned that relevant papers may have been missed. Test Embase searches run by the EAG suggest that a revised and expanded conditions facet combined with both the existing facets for *RET* mutations, or the named interventions of interest could have been conducted without resulting in unmanageable numbers, thus strengthening the validity of the search results.
- Searches included study design filters for RCTs and single arm studies. Given the low numbers, one option to make the search more sensitive may have been to drop the study design filter; the use of study design filters may have resulted in other, potentially relevant, data sources (e.g., registry studies) being missed.
- The EAG noted that Line #1 for each strategy, which contained a subject heading for thyroid neoplasms, appeared to have been excluded from all final line combinations. The company explained that this string was not considered as the focus was on specific histological subtypes of thyroid cancer: medullary thyroid cancer (MTC), papillary thyroid cancer (PTC) and differentiated thyroid cancer (DTC). Given the low number of hits retrieved, the EAG suggests that a broader conditions facet including the subject heading would have been a more cautious approach (see above) and would not have resulted in numbers beyond what would be deemed feasible within the timeframe of the managed access agreement.
- The same search strategy appears have been used across MEDLINE, Embase and the Cochrane Library without translation. The search contains a mix of Medical Subject Headings (MeSH) and Emtree terms, as well a study design filter which is not appropriate in Cochrane Central Register of Controlled Trials (CENTRAL) or Cochrane Database of Systematic Reviews (CDSR), as these are pre-filtered resources, it is unclear what impact this may have had on the overall recall of results, but this may have resulted in unnecessarily restricting the results retrieved by these resources. Whilst most of the subject headings appear to have mapped successfully, this may not always be the case and is not recommended.
- Conference proceedings were searched (from 2019 to 2023). Full details of the conferences searched, search strategies or search terms used, and results were not reported in the CS, but full details were provided in response to the EAG clarification letter.[1]
- Trials registers were searched (2019, 2020, 2022 & 2023). Whilst example search terms were provided it was unclear if these were the complete strategies, and results per resource were not reported in the CS. Full details of the trials register searches were provided in response to the EAG clarification letter.[1]
- The EAG noted that the numbers in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the update searches 2-4 did not appear to match the totals in the

search strategies. This was queried with the company who confirmed that this was a reporting error and provided a corrected PRISMA flow chart.

3.1.2 Inclusion criteria

The eligibility criteria used in the SLR of evidence for selpercatinib and comparators are presented in Table 3.4. Studies were assessed for inclusion by two reviewers, independently; any disagreements were resolved by a third reviewer.[11]

Table 3.4: Eligibility criteria used in for SLR of clinical trial evidence for selpercatinib and comparators

Criteria	Included	Excluded
Population and study type	Single-arm studies included only if report *RET*-altered TC or RCTs in TC (including MTC, PTC, and DTC), or systematic reviews	Single-arm trials in patients without *RET* alterations
Intervention	Selpercatinib (Loxo-292) Pralsetinib (Blu667) **MTC** Cabozantinib Vandetanib Best supportive care **PTC** Sorafenib Lenvatinib Best supportive care	Studies that do not include any of the interventions of interest in at least one study arm
Comparator	Any active systemic therapy, placebo, best supportive care, or no treatment	Studies comparing an intervention of interest with nonpharmacological treatments (e.g., surgery, complementary therapy)
Outcomes	At least one of the following outcomes: Response PFS OS Safety	Studies that do not report at least one of the outcomes of interest
Time Frame	SLR1: January 2015-September 2019 SLR2: September 2019-October 2020 SLR3: October 2020-July 2021 SLR4: July 2021-September 2022 SLR5: September 2022-May 2023	None
Language	English	Any other language

Based on Table 15 in Appendix D of the CS[11]
CS = company submission; DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; OS = overall survival; PFS = progression-free survival; PTC = papillary thyroid cancer; RCT = randomised controlled trials; *RET* = rearrangements and/or mutations during transfection; SLR = systematic literature review; TC = thyroid cancer

EAG comment: The EAG notes that, because only one single arm study of selpercatinib was included, all sources of comparator data were treated as single arm studies and were used, in ITCs, to generate estimates of the comparative efficacy of selpercatinib versus BSC, i.e., only one arm (placebo as a surrogate for BSC) of included RCTs was used. The EAG, therefore, does not consider that it was appropriate to apply different population inclusion criteria for RCTs and single arm studies. Similarly, because included RCTs were used as a source of comparator data only (placebo as a surrogate for BSC), the EAG does not consider that it was appropriate to limit the inclusion of RCTs by active comparator assessed. The EAG considers that these limitations in the design of the SLR mean that potential sources of comparator data have not been adequately explored. Inadequate exploration of potential sources of comparator data is of particular concern given that neither of the two RCTs used as sources of comparator data in the ITCs (Section 3.3) were conducted in, or reported separate data for, populations that matched the decision problem.

3.1.3 Critique of data extraction

Data were extracted by one reviewer and checked by a second reviewer.[11]

EAG comment: The EAG considers that appropriate methods were used to minimise the potential for error and bias in the study selection and data extraction processes.

3.1.4 Quality assessment

Risk of bias assessments, using criteria appropriate to study design, were reported for all studies included in the SLR.[11]

EAG comment: The EAG notes that the risk of bias assessments undertaken for the two RCTs, which were used to provide comparator data for ITCs, are of limited relevance since these studies were not used as RCTs in the context of this appraisal.

3.1.5 Evidence synthesis

Details of the studies included in the SLR, along with a PRISMA flow chart were provided in Appendix D of the CS, Figure 1 and Table 16.[11] Tables 17 and 18, in Appendix D of the CS provide details of the assessment of included studies for inclusion in ITCs of selpercatinib versus BSC for the *RET*-mutant MTC and *RET* fusion-positive TC populations, respectively.[11] Sections B.2.6, B.2.7 and B.2.10 of the CS provide a narrative summary of the clinical effectiveness and safety results of the LIBRETTO-001 study, the only included study of selpercatinib.[5]

EAG comment: The EAG notes that the number of unique included studies given in the PRISMA flow chart and accompanying text (n=24) does not match the number of studies reported in the 'Study characteristics for included studies' table (n=18). The EAG further notes that the report of the SLR, provided in Appendix D of the CS, does not include details of excluded studies. During factual accuracy checking, the company noted that the reporting of 18 included studies was an error and confirmed that 24 unique studies had been identified in the clinical SLR; they provided details of these studies (including those that were missing from Table 18, Appendix D of the original submission) and further confirmed that all 24 studies had been included in their feasibility assessment for the ITC.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical effectiveness section of the CS presented data from one study (LIBRETTO-001). LIBRETTO-001 is an ongoing, single arm, open-label, phase I/II study of selpercatinib in patients with advanced solid tumours, including *RET* fusion-positive solid tumours (e.g., non-small-cell lung cancer [NSCLC], thyroid, pancreas, colorectal), *RET*-mutant MTC and other tumours with *RET* activation.[14] Data from two subgroups of LIBRETTO-001, patients with *RET*-mutant MTC who had received prior cabozantinib/vandetanib (n=152) and patients with *RET*-fusion positive TC who had received prior systemic therapy (n=41), are relevant to this assessment; results for these subgroups were reported in the CS. The CS also included clinical effectiveness data for selpercatinib in the any-line *RET*-altered TC (n=65) and any-line MTC (n=295) populations; data for these populations are used in the ITCs presented in the CS and in the cost-effectiveness analyses.[5] Details of the analysis data sets used in this assessment are provided in Table 3.4.

EAG comment: The EAG notes that not all patients in the prior systemic therapy *RET* fusion-positive TC population had received prior treatment with one of the two treatments specified in the NICE scope; 35/41 (85.4%) patients in this group had received prior treatment with sorafenib or lenvatinib.

3.2.1 Design of LIBRETTO-001

The LIBRETTO-001 study comprised 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 (see Table 3.5) were defined and in which the efficacy and safety of selpercatinib was assessed. 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 twice daily (BID).[5] Patients continued selpercatinib dosing in 28-day cycles until progressed disease (PD), unacceptable toxicity, or other reasons for treatment discontinuation. 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 objective response rate (ORR) using Response Evaluation Criteria In Solid Tumours (RECIST) v1.1. Secondary endpoints included DOR, progression-free survival (PFS), overall survival (OS), time to response and time to best response, CBR, adverse events (AEs) of treatment and EORTC-QLQ-C30. A summary of the methodology of the LIBRETTO-001 study is provided in Table 3.6, and Figures 3.1 and 3.2 show the flow of participants through the LIBRETTO-001 study.

The efficacy and safety evidence for selpercatinib presented in Section B.2 of the CS informed by the most recent data cut for *RET*-altered TC and MTC in the LIBRETTO-001 trial: the 13 January 2023 data cut-off (DCO).

Enrolment into the LIBRETTO-001 trial ended on 1 February 2024; enrolment of the prior cabozantinib/vandetanib *RET*-mutant MTC population ended on 7 June 2019, and enrolment of the prior systemic therapy *RET* fusion-positive TC ended on 1 July 2022. Although the LIBRETTO-001 trial is still ongoing, [redacted][5]

Table 3.5: Analysis set definitions

Trial name	LIBRETTO-001
***RET*-mutant MTC**	
MTC any-line population (n=295)	All efficacy eligible* patients with *RET*-mutant MTC. This patient population was comprised of the MTC:Cab/VanNaïve and MTC:Cab/Van patient populations.
MTC:Cab/Van (n=152)	Efficacy eligible* 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* patients with *RET* fusion-positive TC. This patient population was comprised of the TC:TrtSysNaïve and TC:TrtSys patient populations.
TC:TrtSys (n=41)	Efficacy eligible* 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 13 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 13 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 13 January 2023 DCO

Based on Table 5 in the CS[5]
* 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 13 January 2023 were considered eligible for efficacy analyses.
CS = company submission; DCO = data cut-off; MTC = medullary thyroid cancer; MTC:Cab/Van = prior cabozantinib/vandetanib *RET*-mutant MTC population; OSAS = overall safety analysis set; *RET* = rearranged during transfection; TC = thyroid cancer; TC:TrtSys = prior systemic therapy *RET* fusion-positive TC population

Table 3.6: 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.
Based on Table 4 in the CS[5] CS = company submission; DNA = deoxyribonucleic acid; MTC = medullary thyroid cancer; NSCLC = non-small-cell lung cancer; *RET* = rearranged during transfection	

Table 3.7: Summary of LIBRETTO-001 study 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). 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) Red blood cell 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 proton pump inhibitors (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 independent review committee (IRC) assessment using RECIST v1.1
Secondary and exploratory outcomes	Secondary endpoints Phase I Determination of the safety and tolerability of selpercatinib, characterisation of the pharmacokinetic 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 prior cabozantinib/vandetanib *RET*-mutant MTC and prior systemic therapy *RET* fusion-positive TC populations: • 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 9 May 2017. At the latest DCO (13 January 2023), the median duration of follow-up for OS was 46.9 months and 36.9 months 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.
Based on Table 6 in the CS[5]	

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; CBR = clinical benefit rate; CEA = carcinoembryonic antigen; cfDNA = circulating free DNA; Cmax = maximum drug concentration; CNS = central nervous system; CS =company submission; CYP3A4 = cytochrome P450 3A4; DCO = data cut-off; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation 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; PCR = polymerase chain reaction; 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; RECIST v1.1 = response evaluation criteria in solid tumours, version 1.1; *RET* = rearranged during transfection; RP2D = recommended Phase II dose; SAE = serious adverse event; SFU = safety follow-up; TC = thyroid cancer; TEAE = treatment emergent adverse event; Tmax = time to maximum plasma concentration

Figure 3.1: CONSORT diagram for the *RET*-mutant MTC populations (13 January 2023 DCO) in LIBRETTO-001

Based on Figure 8 in the CS[5]
Cab = cabozantinib; CS = company submission; DCO = data cut-off; MTC = medullary thyroid cancer; *RET* = rearranged during transfection; N = number of patients; Van = vandetanib

Figure 3.2: CONSORT diagram for the *RET* fusion-positive TC populations (13 January 2023 DCO) in LIBRETTO-001

Based on Figure 9 in the CS[5]
CS = company submission; DCO = data cut-off; MTC = medullary thyroid cancer *RET* = rearranged during transfection; N = number of patients; NSCLC = non-small-cell lung cancer; TC = thyroid cancer; TC:TrtSys = Prior systemic therapy RET fusion-positive TC population

3.2.2 Patient disposition in the LIBRETTO-001 study

3.2.2.1 RET-mutant medullary thyroid cancer

A summary of the patient disposition of the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population is provided in Table 3.7.

Of the 152 patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population, [redacted]/152 [redacted] were still on treatment as of the 13 January 2023 DCO, a lower proportion than was the case for the any-line *RET*-mutant MTC population, [redacted]295 [redacted] of whom were still on treatment as of the 13 January 2023 DCO. The most common reason for treatment discontinuation, in both populations was [redacted].[5] The CS states that: *"the frequencies of reasons for treatment discontinuation and study discontinuations were broadly aligned between the populations."*

EAG comment: The EAG notes that the proportion of patients who [redacted] in the prior cabozantinib/vandetanib *RET*-mutant MTC population than in the any-line *RET*-mutant MTC population. The proportions of [redacted] in the prior cabozantinib/vandetanib *RET*-mutant MTC population than in the any-line *RET*-mutant MTC population. The EAG, therefore does not agree that: *"the frequencies of reasons for treatment discontinuation and study discontinuations were broadly aligned between the populations."*

Table 3.8: Patient disposition of *RET*-mutant MTC patients in the LIBRETTO-001 trial

Patient category	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
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]

Based on Table 15 in the CS[5]
CS = company submission; MTC = medullary thyroid cancer; N = number of patients in population; n = number of patients; *RET* = rearranged during transfection

3.2.2.2 RET fusion-positive thyroid cancer

A summary of the patient disposition of the prior systemic therapy *RET* fusion-positive TC population and the any-line *RET* fusion-positive TC population is provided in Table 3.9.

Table 3.9: Patient disposition of *RET* fusion-positive TC patients in the LIBRETTO-001 trial

Patient category	*RET* fusion-positive TC prior systemic therapy N=41	*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]

Based on Table 16 in the CS[5]
[a] At the 13 January 2023 DCO, [redacted] patients were still continuing treatment
CS = company submission; DCO = data cut-off; N = number of patients in population; n = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

Of the 41 patients in the prior systemic therapy *RET* fusion-positive TC population [redacted]41 [redacted] were still on treatment as of the 13 January 2023 DCO, a lower proportion than was the case for the any-line *RET* fusion-positive TC population, [redacted]65 [redacted] of whom were still on treatment as of the 13 January 2023 DCO. The most common reason for treatment discontinuation, in both populations was [redacted].[5]

EAG comment: As was the case for the *RET*-mutant MTC population, the EAG notes that the proportion of patients who [redacted] in the prior systemic therapy *RET* fusion-positive TC population than in the any-line *RET* fusion-positive TC population. The proportion of [redacted] in the prior systemic therapy *RET* fusion-positive TC population than in the any-line *RET* fusion-positive TC population.

3.2.3 Patient characteristics in the LIBRETTO-001 study

3.2.3.1 RET-mutant medullary thyroid cancer

The baseline demographics and disease characteristics of the prior cabozantinib/vandetanib *RET*-mutant MTC population (N=152) and the any-line *RET*-mutant MTC population (N=295) in the LIBRETTO-001 trial are presented in Table 3.9. A summary of prior cancer-related treatments for the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population in the LIBRETTO-001 trial is provided in Table 3.10.

The median age of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population was 58.0 years, with a wide range of patient ages (17–90 years). The prior cabozantinib/vandetanib *RET*-mutant MTC population included more males (63.8%) than females (36.2%) and the majority of the population were White (90.1%).[5]

For the prior cabozantinib/vandetanib *RET*-mutant MTC population (N=152), the median time from diagnosis at the 13th January 2023 DCO was [redacted] months; the majority of patients (92.8%) 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.[5]

The CS states that: *"The baseline characteristics of the MTC any-line population were closely aligned with characteristics of the prior cabozantinib/vandetanib RET-mutant MTC population."*

EAG comment: The EAG notes that the prior cabozantinib/vandetanib *RET*-mutant MTC population included a lower proportion of patients with ECOG performance status 0, 42/152 (27.6%), than the any-line *RET*-mutant MTC population, 111/295 (37.6%). In addition, the proportion of patients with CNS metastases was [redacted].

Table 3.10: Baseline demographics and disease characteristics of patients with *RET*-mutant MTC in the LIBRETTO-001 study

Characteristic	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
Age, years		
Median	58.0	58.0
Mean	[redacted]	[redacted]
Range	17–90	15–90
Overall age group, n (%)		
12 to <45 years[a]	[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	97 (63.8)	180 (61.0)
Female	55 (36.2)	115 (39.0)

Characteristic	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
Race, n (%)		
White	137 (90.1)	261 (88.5)
Black or African American	2 (1.3)	4 (1.4)
Asian	2 (1.3)	10 (3.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)
American Indian or Alaska Native	1 (0.7)	1 (0.3)
Other	10 (6.6)	17 (5.8)
Missing	0 (0.0)	1 (0.3)
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	42 (27.6)	111 (37.6)
1	99 (65.1)	167 (56.6)
2	11 (7.2)	17 (5.8)
Stage at entry, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	141 (92.8)	[redacted]
Missing	[redacted]	[redacted]
Time from initial diagnosis, months		
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

Characteristic	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
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	11 (7.2)	14 (4.7)
***RET* mutation type, n (%)**		
M918T	99 (65.1)	185 (62.7)
V804 M/L	8 (5.3)	14 (4.7)
Extracellular Cysteine Mutation	24 (15.8)	58 (19.2)
Other	21 (13.8)	38 (12.9)

Based on Tables 7 and 13 in the CS[5]
[a] [redacted] in the prior cabozantinib/vandetanib *RET*-mutant MTC population and [redacted] in the any-line *RET*-mutant MTC population were less than 18 years old.
CEA = carcinoembryonic antigen; CNS = central nervous system; CS = company submission; ECOG = Eastern Cooperative Oncology Group; MTC = medullary thyroid cancer; N = number of patients in efficacy population; n = number of patients; *RET* = rearranged during transfection

In the prior cabozantinib/vandetanib *RET*-mutant MTC patient population, all patients had received prior treatment with cabozantinib, vandetanib or both. Overall, 83/152 (54.6%) patients had previously received cabozantinib and 120/152 (78.9%) patients had received vandetanib, with 51/152 (33.6%) patients previously receiving both cabozantinib and vandetanib. Furthermore, nine (5.9%) patients had received sorafenib and 15 (9.9%) patients had received lenvatinib. Additionally, 16 (10.5%) patients had received 'other' types of systemic therapy, including radioactive iodine and mammalian target of rapamycin (mTOR) inhibitors.

Table 3.11: Prior cancer-related treatments for patients with *RET*-mutant MTC in the LIBRETTO-001 study

Prior treatment	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
Received prior systemic therapy, n (%)		
Yes	152 (100.0)	179 (60.7)
No	0 (0.0)	116 (39.3)
Type of prior systemic therapy, n (%)		
MKI	152 (100.0)	161 (54.6)
Cabozantinib	83 (54.6)	83 (28.1)
Vandetanib	120 (78.9)	120 (40.7)
Both cabozantinib and vandetanib	[redacted]	[redacted]
Sorafenib	9 (5.9)	13 (4.4)
Lenvatinib	15 (9.9)	18 (6.1)
Other MKIs	21 (13.8)	23 (7.8)
Other	16 (10.5)	25 (8.5)
Radioactive iodine	0 (0.0)	2 (0.7)
mTOR inhibitor	4 (2.6)	5 (1.7)
VEGF/VEGFR inhibitor	1 (0.7)	0 (0.0)
Selective *RET* inhibitor	1 (0.7)	1 (0.3)
Hormonal therapy	0 (0.0)	1 (0.3)
Other systemic therapy	12 (7.9)	2 (0.7)
Number of prior systemic regimens, n (%)		
0	0 (0.0)	116 (39.3)
1	73 (48.0)	95 (32.2)
2	37 (24.3)	42 (14.2)
≥3	42 (27.6)	42 (14.2)
Prior systemic regimens		
Median	2.0	[redacted]
Range	1–8	[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]
Based on Table 8 in the CS[5]		

Prior treatment	*RET*-mutant MTC prior cabozantinib/vandetanib N=152	*RET*-mutant MTC any-line population N=295
CS = company submission; MKI = multikinase inhibitor; MTC = medullary thyroid cancer; mTOR = mammalian target of rapamycin; N = number of patients in population; n = number of patients; *RET* = rearranged during transfection; VEGF/VEGFR = vascular endothelial growth factor/vascular endothelial growth factor receptor		

3.2.3.2 RET fusion-positive thyroid cancer

The baseline demographics and the disease characteristics of the prior systemic therapy *RET* fusion-positive TC (N=41) and the any-line *RET* fusion-positive TC (N=65) patient populations enrolled in the LIBRETTO-001 trial are presented in Table 3.12. Prior cancer-related treatments in these populations are also presented in Table 3.12.[5]

The prior systemic therapy *RET* fusion-positive TC population included four different thyroid histological subtypes; the majority of patients were diagnosed with papillary TC (N=31; 75.6%), with five cases of poorly differentiated TC (N=5; 12.2%), four cases of anaplastic TC (N=4; 9.8%) and one case of Hürthle cell TC (N=1; 2.4%) observed.[5]

Median age for the prior systemic therapy *RET* fusion-positive TC population was 58.0 years, also featuring a wide age range of 25–88 years. There were more females (56.1%) than males (43.9%) in the patient population, and the majority of patients (58.5%) were White.[5]

The median time from initial diagnosis was [redacted] months for the prior systemic therapy *RET* fusion-positive TC population. [redacted] had metastatic disease at enrolment, with a median time since diagnosis of metastatic disease of [redacted] months. The majority of patients had Stage IV disease at entry to the study (87.8%).[5]

The CS states that: *"Baseline demographic characteristics were broadly aligned between the any-line RET fusion-positive TC population and the prior systemic therapy RET fusion-positive TC population."*

EAG comment: The EAG notes that the prior systemic therapy *RET* fusion-positive TC population included a lower proportion of patients with ECOG performance status 0, 11/41 (26.8%), than the any-line *RET* fusion-positive TC population, 25/65 (38.5%). In addition, the proportion of patients with CNS metastases was higher in the prior systemic therapy *RET* fusion-positive TC population, 12/41 (29.3%), than in the any-line *RET* fusion-positive TC population, 13/65 (20.0%). The distribution of histological subtypes also differed between the two populations.

Table 3.12: Baseline demographics and disease characteristics of patients with *RET* fusion-positive TC in the LIBRETTO-001 study

Characteristic	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] N=65
Age, years		
Median	58.0	59.0
Mean	[redacted]	[redacted]
Range	25–88	20–88
Overall age group, n (%)		
18 to <45 years	[redacted]	[redacted]

Characteristic	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] N=65
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	18 (43.9)	32 (49.2)
Female	23 (56.1)	33 (50.8)
Race, n (%)		
White	24 (58.5)	42 (64.6)
Black	3 (7.3)	3 (4.6)
Asian	12 (29.3)	13 (20.0)
Other	2 (4.9)	5 (7.7)
Missing	0 (0.0)	2 (3.1)
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	11 (26.8)	25 (38.5)
1	27 (65.9)	36 (55.4)
2	3 (7.3)	4 (6.2)
Smoking history, n (%)		
Never smoked	28 (68.3)	40 (61.5)
Former smoker	13 (31.7)	23 (35.4)
Current smoker	0 (0.0)	1 (1.5)
Missing	0 (0.0)	1 (1.5)

Characteristic	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population[a] N=65
Primary tumour type, n (%)		
Papillary thyroid	31 (75.6)	54 (83.1)
Poorly differentiated thyroid	5 (12.2)	6 (9.2)
Anaplastic thyroid	4 (9.8)	4 (6.2)
Hürthle cell thyroid	1 (2.4)	1 (1.5)
Stage at entry, n (%)		
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	36 (87.8)	[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	12 (29.3)	13 (20.0)
***RET* fusion type (n, %)**		
CCDC6	25 (61.0)	40 (61.5)
NCOA4	8 (19.5)	15 (23.1)
Other	7 (17.1)	9 (13.8)
Unknown	1 (2.4)	1 (1.5)

Based on Tables 9, 10 and 14 in the CS[5]
CNS = central nervous system; CS = company submission; ECOG = Eastern Cooperative Oncology Group; N = number of patients in population; n = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

Of the 41 patients in the prior systemic therapy *RET*-fusion positive TC population, 35/41 (85.4%) had received a prior treatment regimen specified in the original NICE guidance for selpercatinib in this indication (TA742). The majority of patients had previously received lenvatinib (N=26; 63.4%) and nine patients had previously received sorafenib (N=9; 22.0%); of these patients, four (9.8%) patients had received both lenvatinib and sorafenib. Additionally, one patient had previously received

cabozantinib (N=1; 2.4%) and one patient had previously received vandetanib (N=1; 2.4%). Of the prior systemic therapy *RET*-fusion positive TC patients, 30/41 (73.2%) patients had received systemic radioactive iodine as a prior therapy.

The EAG notes an inconsistency in the data presented for the numbers of patients in the prior systemic therapy *RET*-fusion positive TC population who had previously received lenvatinib, sorafenib, or both; if, as indicated N=26 had received lenvatinib, N=9 had received sorafenib and N=4 had received both, then the total number of patients who received prior TKI treatment, in line with the original NICE guidance for selpercatinib in this indication (TA742) would be N=31 not N=35; this would also be the number of patients who had received prior TKI treatment in line with current UK clinical practice and the scope for this assessment.

Table 3.13: Prior cancer-related treatments for patients with *RET* fusion-positive TC in the LIBRETTO-001 study

Prior treatment	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population N=65
Received prior systemic therapy, n (%)		
Yes	41.0 (100.0)	53 (81.5)
Type of prior systemic therapy, n (%)		
MKI	35 (85.4)	35 (53.8)
Cabozantinib	1 (2.4)	1 (1.5)
Vandetanib	1 (2.4)	1 (1.5)
Sorafenib	9 (22.0)	9 (13.8)
Lenvatinib	26 (63.4)	26 (40.0)
Other MKIs	7 (17.1)	7 (10.8)
Chemotherapy	8 (19.5)	8 (12.3)
Platinum	4 (9.8)	4 (6.2)
Taxane	5 (12.2)	5 (7.7)
Immunotherapy	3 (7.3)	3 (4.6)
Other	30 (73.2)	48 (73.8)
mTOR inhibitor	2 (4.9)	2 (3.1)
EGFR inhibitor	1 (2.4)	1 (1.5)
Radioactive iodine therapy	30 (73.2)	48 (73.8)
Other systemic therapy	4 (9.8)	4 (6.2)
Number of prior systemic regimens, n (%)		
0	0 (0.0)	6 (9.2)
1	10 (24.4)	20 (30.8)
2	8 (19.5)	11 (16.9)
≥3	23 (56.1)	28 (43.1)
Prior systemic regimens		
Median	3.0	[redacted]
Range	1–7	[redacted]
Best response to last systemic treatment, n (%)		
Complete response	[redacted]	[redacted]

Prior treatment	*RET* fusion-positive TC prior systemic therapy N=41	*RET* fusion-positive TC any-line population N=65
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]

Based on Table 11 in the CS[5]
CS = company submission; EGFR = epidermal growth factor receptor; MKI = multikinase inhibitor; mTOR = mammalian target of rapamycin; N = number of patients in population; n = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

3.2.4 Quality of the LIBRETTO-001 study

The CS reports that the LIBRETTO-001 study was assessed for risk of bias and generalisability, in-line with NICE requirements;[5] Table 3.14 summarises the results of this assessment.

Table 3.14: Quality assessment of the LIBRETTO-001 trial

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 assessed using common terminology criteria for adverse events (CTCAE). Neither the patients nor the outcome assessor was blinded as the trial is an open-label, single-arm study.
5A. Have the authors identified all important confounding factors?	NA – LIBRETTO-001 is a single-arm trial.

Study Question	Grade (yes/no/unclear)
List the ones you think might be important, that the author missed.	
5B. Have they taken account of the confounding factors in the design and/or analysis?	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 13 January 2023 data cut, median duration of follow-up for OS was 44.6 months and 38.7 months 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.
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 13 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 available via routine commissioning for patients with *RET*-altered tumours in the second-line; selpercatinib is currently available through the CDF.
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.

Based on Table 19 in the CS[5]

CDF = cancer drugs fund; CS = company submission; CSR = clinical study report; CTCAE = common terminology criteria for adverse events; DCO = data cut-off; IRC = independent review committee; MKI = multikinase inhibitors; MTC = medullary thyroid cancer; MTD = maximum-tolerated dose; NA = 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

The CS states that: *"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. 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."*[5]

EAG comment: The EAG generally agrees with the findings of risk of bias assessment conducted for the LIBRETTO-001 study. However, the EAG does not agree that the findings of this study are generalisable to the UK, with respect to the populations specified in the current decision problem; this is because the prior treatments received by some participants in LIBRETTO-001 study were not consistent with UK clinical practice. Subgroup analyses for populations, which matched the decision problem and UK clinical practice for prior treatments, were provided by the company in their response to clarification questions.

3.2.5 Effectiveness results of the LIBRETTO-001 study

The CS included results, from LIBRETTO-001, for the primary outcome measure ORR based on independent review committee (IRC) assessment using RECIST v1.1 and for secondary outcome measures, which included all outcomes specified in the NICE scope (OS, PFS and HRQoL). The CS also included results for additional outcomes, not specified in the NICE scope, (DOR, time to best response, CBR).

3.2.5.1 Primary outcome ORR by RECIST v1.1

Objective response rate was defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR). Best overall response was defined as the best response designation for each patient recorded between the date of the first dose of selpercatinib and the DCO (13 January 2023), or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery.[5]

3.2.5.1.1 RET-mutant medullary thyroid cancer

Independent review committee assessed ORR and BOR for the prior cabozantinib/vandetanib, prior cabozantinib or vandetanib and the any-line *RET*-mutant MTC populations are presented in Table 3.15.

For patients with *RET*-mutant MTC who had received prior cabozantinib/vandetanib, ORR was 77.6% (118/152, 95% CI: 70.2, 84.0), with 19/152 (12.5%) of patients achieving CR and 99/152 (65.1%) patients achieving PR. Clinical benefit rate and disease control rate (DCR) were high in the prior cabozantinib/vandetanib *RET*-mutant MTC population, with rates of 91.4% (95% CI: 85.8, 95.4) and 94.1% [redacted] respectively.[5] For patients with *RET*-mutant MTC who had received prior cabozantinib or vandetanib (in-line with the decision problem), ORR was [redacted], with [redacted] of patients achieving CR and [redacted] patients achieving PR.[1]

The CS states that: *"BOR and ORR results for the any- line MTC population were consistent with the prior cabozantinib/vandetanib RET-mutant MTC population."*

EAG comment: The EAG notes that the ORR was higher in the *RET*-mutant MTC any-line population, 236/295 (80%) than in the *RET*-mutant MTC prior cabozantinib/vandetanib population, 118/152 (77.6%), though [redacted] to that provided for the *RET*-mutant MTC prior cabozantinib **or** vandetanib population, [redacted]. The EAG further notes that a [redacted] proportion of patients in the *RET*-mutant MTC any-line population, 53/295 (18.0%), achieved a BOR category of CR than in the *RET*-mutant MTC prior cabozantinib/vandetanib population or the *RET*-mutant MTC prior cabozantinib **or** vandetanib population. The EAG therefore questions whether the ORR and BOR results can be described as consistent across populations with differing prior treatments.

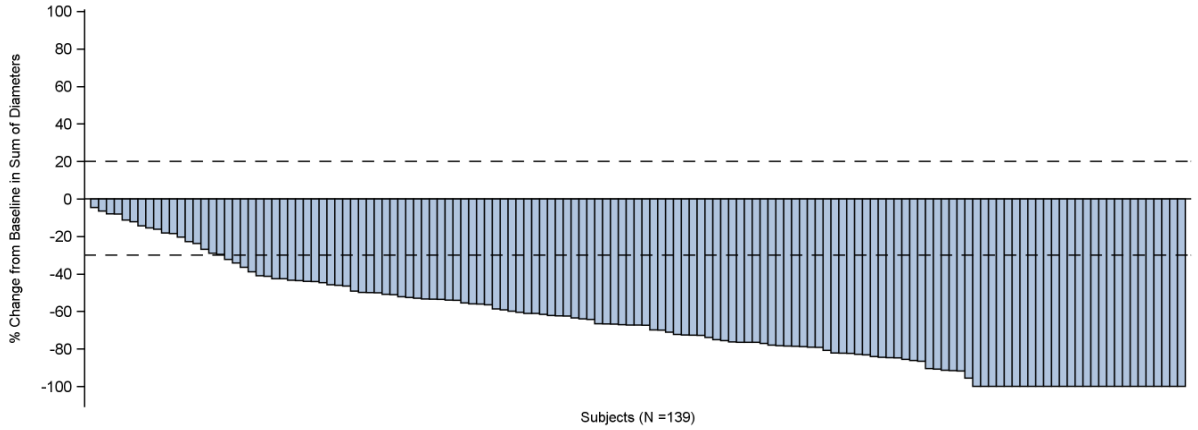
Table 3.15: ORR and BOR based on IRC assessment for the prior cabozantinib/vandetanib and any-line *RET*-mutant MTC populations in the LIBRETTO-001 study

Outcome measure	*RET*-mutant MTC prior cabozantinib or vandetanib[a] [redacted]	*RET*-mutant MTC prior cabozantinib/vandetanib[b] N=152	*RET*-mutant MTC any-line population N=295
ORR[c]			
n (%)	[redacted]	118 (77.6)	236 (80.0)
95% CI	[redacted]	(70.2, 84.0)	[redacted]
BOR, n (%)			
CR	[redacted]	19 (12.5)	53 (18.0)
PR	[redacted]	99 (65.1)	183 (62.0)
SD	[redacted]	25 (16.4)	45 (15.3)
SD16+	[redacted]	[redacted]	[redacted]
PD	[redacted]	2 (1.3)	4 (1.4)
Not evaluable	[redacted]	7 (4.6)	10 (3.4)
CBR (CR + PR + SD16+)			
n (%)	[redacted]	139 (91.4)	274 (92.9)
95% CI	[redacted]	(85.8, 95.4)	[redacted]
DCR (CR + PR + SD)			
n, (%)	[redacted]	143 (94.1)	281 (95.3)
95% CI	[redacted]	[redacted]	[redacted]

Based on Table 20 in the CS[5] and Table 9 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both cabozantinib and vandetanib
[c] Response was confirmed by a repeat assessment every ≥28 days
BOR = best overall response; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; CS = company submission; DCR = disease control rate; IRC = independent review committee; MTC = medullary thyroid cancer; N = number of patients in the population; n = number of patients per category; 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

Waterfall plots illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment for the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are shown below in Figure 3.3 and Figure 3.4, respectively, indicating that tumours were reduced by >25% for the majority of patients in both populations.[5]

Figure 3.3: Waterfall plot of best change in tumour size based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population



Based on Figure 10 in the CS[5]
13 patients are not shown, due to seven patients having non-target lesions only and six patients without postbaseline target lesion measurement.
CS = company submission; IRC = independent review committee; MTC = medullary thyroid cancer; N = number of patients; *RET* = rearranged during transfection

Figure 3.4: Waterfall plot of best change in tumour size based on IRC assessment for any-line patients with *RET*-mutant MTC

Based on Figure 11 in the CS[5]
[redacted] patients are not shown, due to [redacted] patients having non target lesions only and [redacted] patients without post-baseline target lesion measurement.
CS = company submission; IRC = independent review committee; MTC = medullary thyroid cancer; N = number of patients; *RET* = rearranged during transfection

3.2.5.1.2 RET fusion-positive thyroid cancer

Results for IRC-assessed ORR and BOR for the prior systemic therapy *RET*-fusion positive TC population, the prior lenvatinib or sorafenib *RET*-fusion positive TC population and the any-line *RET* fusion-positive TC population are presented in Table 3.16.

For the prior systemic therapy *RET* fusion-positive TC population, ORR was 85.4% (35/41, 95% confidence interval (CI): 70.8, 94.4), with 5/41 (12.2%) patients experiencing a CR and 30/41 (73.2%) patients experiencing a PR. Clinical benefit rate and DCR were both high in the prior systemic therapy *RET* fusion positive TC population, both with rates of 100.0% (41/41, 95% CI: 91.4, 100.0). For patients with *RET* fusion-positive TC population who had received prior lenvatinib **or** sorafenib (in-line with

the decision problem), ORR was [redacted], with [redacted] experiencing a CR and [redacted] experiencing a PR.[1]

The CS states that: *"BOR and ORR results were similar in the any-line RET fusion-positive TC patient population compared to the prior systemic therapy RET fusion-positive TC population."*

EAG comment: The EAG notes that the ORR was higher in the *RET* fusion-positive TC any-line population, 58/65 (89.2%) than that seen in the *RET* fusion-positive prior systemic therapy population and in the *RET* fusion-positive TC population who had received prior lenvatinib **or** sorafenib. The EAG further notes that a higher proportion of patients in the *RET* fusion-positive TC any-line population, 10/65 (15.4%), achieved a BOR category of CR than in the *RET* fusion-positive prior systemic therapy population and in the *RET* fusion-positive TC population who had received prior lenvatinib **or** sorafenib. The EAG therefore questions whether the ORR and BOR results can be described as consistent across populations with differing prior treatments.

Table 3.16: ORR and BOR based on IRC assessment for patients with *RET*-fusion positive TC in the LIBRETTO-001 study

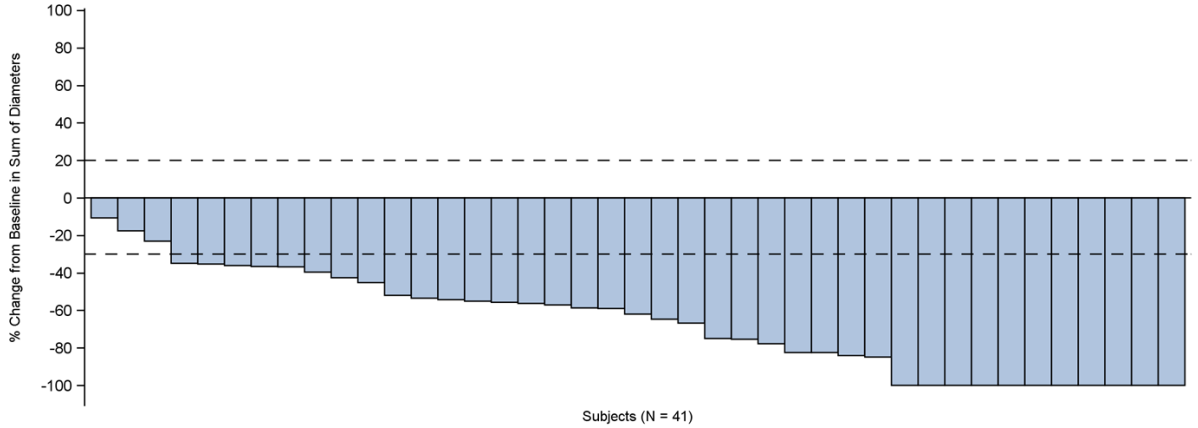
Outcome measure	*RET* fusion-positive TC prior treatment with lenvatinib or sorafenib[a] [redacted]	*RET* fusion-positive TC prior systemic therapy[b] N=41	*RET* fusion-positive TC any-line population N=65
ORR[c]			
n (%)	[redacted]	35 (85.4)	58 (89.2)
95% CI	[redacted]	(70.8, 94.4)	[redacted]
BOR, n (%)			
CR	[redacted]	5 (12.2)	10 (15.4)
PR	[redacted]	30 (73.2)	48 (73.8)
SD	[redacted]	6 (14.6)	7 (10.8)
SD16+	[redacted]	[redacted]	[redacted]
PD	[redacted]	0 (0.0)	0 (0.0)
Not evaluable	[redacted]	0 (0.0)	0 (0.0)
CBR (CR + PR + SD16+)			
n (%)	[redacted]	41 (100.0)	65 (100.0)
95% CI	[redacted]	(91.4, 100.0)	[redacted]
DCR (CR + PR + SD)			
N, (%)	[redacted]	41 (100.0)	65 (100.0)
95% CI	[redacted]	[redacted]	[redacted]

Based on Table 26 in the CS[5] and Table 13 in the response to clarification questions[1]
[a] Population in-line with the decision problem; [b] Including patients who had previously received both lenvatinib and sorafenib, and patients treated with other systemic therapies; [c] Response was confirmed by a repeat assessment every ≥28 days
BOR = best overall response; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; CS = company submission; DCR = disease control rate; IRC = independent review committee; 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

A waterfall plot illustrating the best change in tumour size per RECIST v1.1 based on IRC assessment for the prior systemic therapy *RET*-fusion positive TC population is also shown in Figure 3.5, indicating

that the sum of diameters of tumours were reduced >25% in all patients but three (N=38). A waterfall plot illustrating this outcome is also provided for the any-line TC patient population in Figure 3.6.[5]

Figure 3.5: Waterfall plot of best change in tumour size based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population



Based on Figure 17 in the CS.[5]
CS = company submission; IRC = independent review committee; N = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 3.6: Waterfall plot of best change in tumour size based on IRC assessment for any-line patients with *RET* fusion-positive TC

[redacted]

Based on Figure 18 in the CS.[5]
CS = company submission; IRC = independent review committee; N = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

3.2.5.2 Secondary outcome, listed in NICE scope, PFS

Progression-free survival 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).[5]

3.2.5.2.1 RET-mutant medullary thyroid cancer

The PFS results, based on IRC assessment, for the prior cabozantinib/vandetanib, prior cabozantinib or vandetanib and the any-line *RET*-mutant MTC populations are presented in Table 3.17

For the prior cabozantinib/vandetanib *RET*-mutant MTC population, after a median duration of follow-up of 44.0 months, median PFS was 41.4 months (95% CI: 30.2, not estimable [NE]). At the DCO, [redacted] in this efficacy set were alive without documented disease progression by IRC assessment.[5] For patients with *RET*-mutant MTC who had received prior cabozantinib **or** vandetanib (in-line with the decision problem), after a median duration of follow-up of [redacted] months, median PFS was [redacted] months (95% CI: [redacted]).[1] At the DCO, [redacted] in this efficacy set were alive without documented disease progression by IRC assessment. The second most common reason for censoring in the prior cabozantinib **or** vandetanib *RET*-mutant MTC population was subsequent anti-cancer therapy or surgery without documented PD [redacted]. Rates of PFS ranged from [redacted] for ≥12 months, to [redacted] at ≥36 months for the prior cabozantinib or vandetanib *RET*-mutant MTC population.[1]

The CS states that: *"PFS results for the any-line RET-mutant MTC population were broadly consistent with the prior cabozantinib/vandetanib RET-mutant MTC population, with PFS landmark rates for the any-line population being slightly higher than the prior cabozantinib/vandetanib RET-mutant MTC population."*[5]

EAG comment: The EAG notes that, at the DCO, [redacted]/295 [redacted] of patients in the any-line *RET*-mutant MTC population were alive without documented disease progression by IRC assessment, compared to [redacted]/152 [redacted] of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population and [redacted] of patients in the prior cabozantinib or vandetanib *RET*-mutant MTC population. The EAG further notes that the rates of PFS were between [redacted] in the any-line *RET*-mutant MTC population than in the prior cabozantinib or vandetanib *RET*-mutant MTC population, for all points recorded (≥12 months, ≥24 months and ≥36 months). The EAG therefore questions whether the PFS results can be described as broadly consistent across populations with differing prior treatments.

Table 3.17: PFS based on IRC assessment for the prior cabozantinib/vandetanib MTC population and the any-line MTC population in the LIBRETTO-001 study

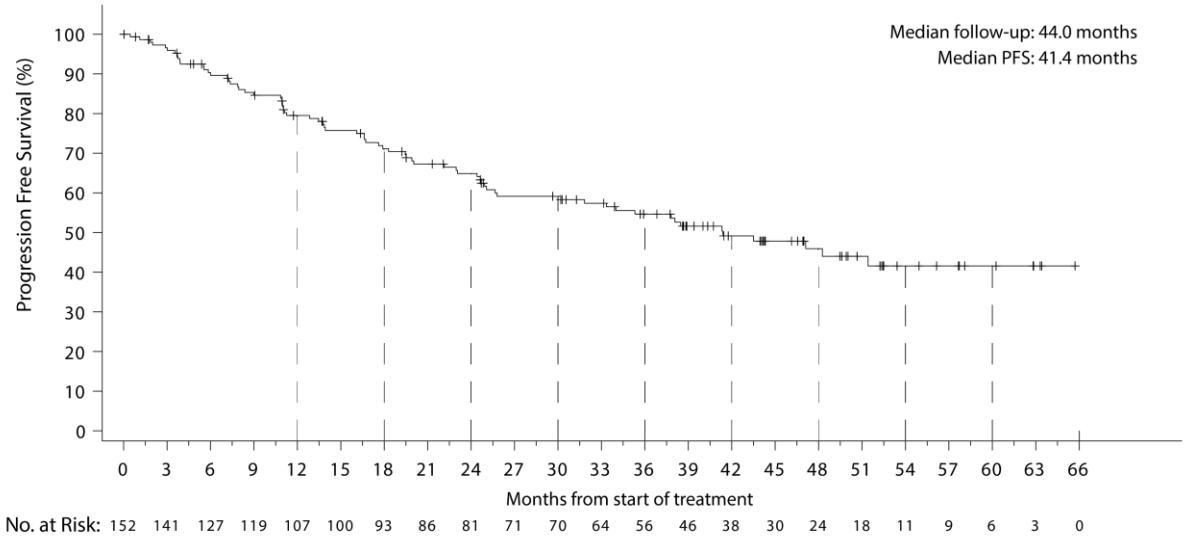
	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib[a] [redacted]**	***RET*-mutant MTC prior cabozantinib/vandetanib[b] N=152**	***RET*-mutant MTC any-line population N=295**
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]

	RET-mutant MTC prior treatment with cabozantinib or vandetanib[a] [redacted]	*RET*-mutant MTC prior cabozantinib/vandetanib[b] N=152	*RET*-mutant MTC any-line population N=295
Duration of PFS (months)			
Median	[redacted]	41.4	[redacted]
95% CI	[redacted]	30.2, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of PFS			
≥12 months or more (95% CI)	[redacted]	79.5 (71.8, 85.3)	[redacted]
≥24 months or more (95% CI)	[redacted]	64.9 (56.2, 72.3)	[redacted]
≥36 months or more (95% CI)	[redacted]	54.6 (45.6, 62.8)	[redacted]
Duration of follow-up (months)			
Median	[redacted]	44.0	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Progression status (n, %)			
Disease progression	[redacted]	53 (34.9)	86 (29.2)
Died (no disease progression beforehand)	[redacted]	16 (10.5)	22 (7.5)
Censored	[redacted]	83 (54.6)	187 (63.4)

Based on Table 22 in the CS[5] and Table 11 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both cabozantinib and vandetanib
'*' denotes where some data have been censored.
CI = confidence interval; CS = company submission; IRC = independent review committee; MTC = medullary thyroid cancer; NE = not estimable; NR = not reported; PD = disease progression; PFS = progression-free survival; *RET* = rearranged during transfection

Kaplan–Meier (KM) plots of PFS for the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are presented in Figures 3.7 and 3.8, respectively.

Figure 3.7: KM plot of PFS based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population



Based on Figure 13 in the CS[5]
CS = company submission; IRC = independent review committee; KM = Kaplan-Meier; MTC = medullary thyroid cancer; No. = number of patients; PFS = progression-free survival; *RET* = rearranged during transfection

Figure 3.8: KM plot of PFS based on IRC assessment for any-line patients with *RET*-mutant MTC

[redacted]

Based on Figure 14 in the CS[5]
CI = confidence interval; CS = company submission; IRC = independent review committee; KM = Kaplan-Meier; MTC = medullary thyroid cancer; NE = not estimable; PFS = progression-free survival; *RET* = rearranged during transfection

3.2.5.2.2 RET fusion-positive thyroid cancer

Progression-free survival results, based on IRC assessment, for the prior systemic therapy, prior lenvatinib *or* sorafenib and the any-line *RET*-fusion positive TC populations are presented in Table 3.18.

For the prior systemic therapy population, after a median follow-up of 30.4 months, median PFS was 27.4 months (95% CI: 14.5, NE).[5] For patients with *RET*-fusion positive TC who had received prior lenvatinib **or** sorafenib (in-line with the decision problem), after a median duration of follow-up of [redacted] months, median PFS was [redacted] months (95% CI: [redacted]).[1] For patients with *RET*-fusion positive TC who had received prior lenvatinib **or** sorafenib, [redacted] were alive without

documented disease progression by IRC assessment at the DCO. Rates of PFS ranged from [redacted] for ≥12 months, to [redacted] at ≥36 months.[1]

The CS states that: *"PFS results were broadly consistent in the any-line TC patient population compared to the prior systemic therapy RET fusion-positive TC population. However, PFS landmark rates for the any-line RET fusion-positive population were slightly higher at later timepoints than the prior systemic therapy RET fusion-positive TC population. Additionally, median PFS was [redacted] (95% CI: [redacted] in the any-line population."*[5]

EAG comment: The EAG notes that, at the DCO, [redacted]/65 [redacted] of patients in the any-line *RET* fusion-positive TC population were alive without documented disease progression by IRC assessment, compared to [redacted]/41 [redacted] of patients in the prior systemic therapy *RET* fusion-positive TC population and [redacted] in the population who had received prior lenvatinib **or** sorafenib. The EAG further notes that the rates of PFS were between [redacted] in the any-line *RET* fusion-positive TC population than in the population who had received prior lenvatinib **or** sorafenib, for all points recorded (≥12 months, ≥24 months and ≥36 months). The EAG therefore questions whether the PFS results can be described as broadly consistent across populations with differing prior treatments.

Table 3.18: PFS based on IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 study

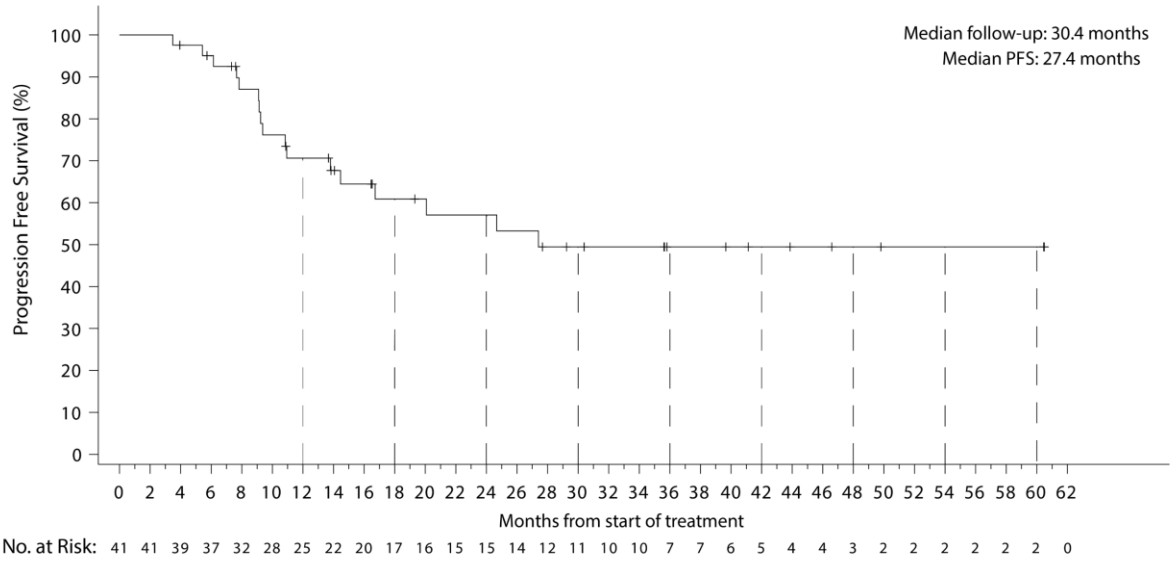
	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib[a]** [redacted]	***RET* fusion-positive TC prior systemic therapy[b] N=41**	***RET* fusion-positive TC any-line population N=65**
Reason censored (n, %)			
Alive without documented disease progression	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]
Duration of PFS (months)			
Median	[redacted]	27.4	[redacted]
95% CI	[redacted]	14.5, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of PFS			
≥12 months or more (95% CI)	[redacted]	70.6 (53.2, 82.6)	[redacted]

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib[a]** [redacted]	***RET* fusion-positive TC prior systemic therapy[b] N=41**	***RET* fusion-positive TC any-line population N=65**
≥24 months or more (95% CI)	[redacted]	57.1 (38.6, 71.8)	[redacted]
≥36 months or more (95% CI)	[redacted]	49.5 (31.1, 65.4)	[redacted]
Duration of follow-up (months)			
Median	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Progression status (n, %)			
Disease progression	[redacted]	16 (39.0)	19 (29.2)
Died (no disease progression beforehand)	[redacted]	1 (2.4)	1 (1.5)
Censored	[redacted]	24 (58.5)	45 (69.2)

Based on Table 28 in the CS[5] and Table 15 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both lenvatinib and sorafenib, and patients treated with other systemic therapies
'*' denotes where some data have been censored
CI = confidence interval; CS = company submission; IRC = independent review committee; NE = not estimable; NR = not reported; PD = disease progression; PFS = progression-free survival; *RET* = rearranged during transfection; TC = thyroid cancer

Kaplan-Meier plots of PFS for the prior systemic therapy and the any-line *RET* fusion-positive TC populations are presented in Figures 3.9 and 3.10, respectively.

Figure 3.9: KM plot of PFS based on IRC assessment for the prior systemic therapy *RET* fusion-positive TC population



Based on Figure 21 in the CS[5]

CS = company submission; IRC = independent review committee; KM = Kaplan-Meier; No. = number of patients; PFS = progression-free survival; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 3.10: KM plot of PFS based on IRC assessment for any-line patients with *RET* fusion-positive TC

Based on Figure 22 in the CS[5]
CS = company submission; IRC = independent review committee; KM = Kaplan-Meier; No.= number of patients; PFS = progression-free survival; *RET* = rearranged during transfection; TC = thyroid cancer

3.2.5.3 Secondary outcome, listed in NICE scope, OS

Overall survival 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.[5]

3.2.5.3.1 RET-mutant medullary thyroid cancer

Overall survival results for the prior cabozantinib/vandetanib, prior cabozantinib or vandetanib and the any-line *RET*-mutant MTC populations are presented in Table 3.19.

The rate of OS for the prior cabozantinib/vandetanib *RET*-mutant MTC population ranged from 87.8% (95% CI: 81.3%, 92.1%) at ≥12 months to 67.8% (95% CI: 59.4%, 74.8%) at ≥36 months.[5] The rate of OS for the prior cabozantinib **or** vandetanib *RET*-mutant MTC population was similar, ranging from [redacted] at ≥12 months to [redacted] at ≥36 months.[1] While median OS was reached in both the prior cabozantinib/vandetanib *RET*-mutant MTC population and prior cabozantinib **or** vandetanib *RET*-mutant MTC population, these results were not considered meaningful due to the relatively short median follow-up duration of 46.9 and [redacted] for OS.[5]

The CS states that: *"OS results for the any-line MTC population were broadly consistent with the prior cabozantinib/vandetanib RET-mutant MTC population, with OS landmark rates for the any-line RET-mutant MTC population being slightly higher at later timepoints than the prior cabozantinib/vandetanib RET-mutant MTC population."*[5]

EAG comment: The EAG notes that, at the DCO, 224/295 (75.9%) of patients in the any-line *RET*-mutant MTC population were alive or lost to follow-up, compared to 96/152 (63.2%) of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population and [redacted] in the prior cabozantinib **or** vandetanib *RET*-mutant MTC population. The EAG further notes that the rates of OS were between [redacted] in the any-line *RET*-mutant MTC population than in the prior cabozantinib **or** vandetanib *RET*-mutant MTC population, for all points recorded (≥12 months, ≥24

months and ≥36 months). The EAG therefore questions whether the OS results can be described as broadly consistent across populations with differing prior treatments.

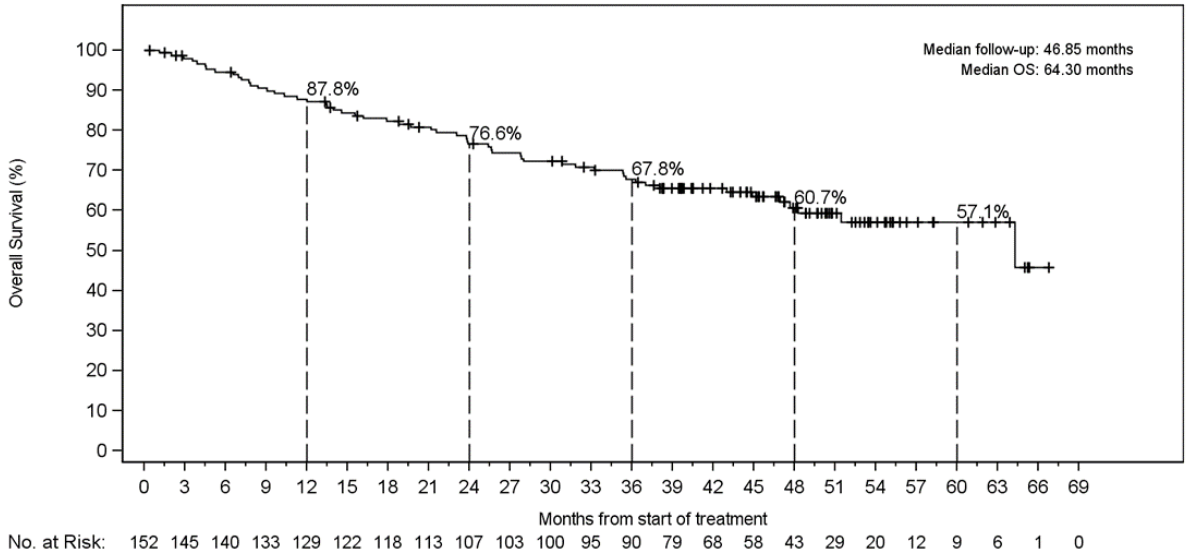
Table 3.19: OS for the prior cabozantinib/vandetanib *RET*-mutant MTC population and the any-line *RET*-mutant MTC population in the LIBRETTO-001 study

	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib[a]** [redacted]	***RET*-mutant MTC prior cabozantinib/vandetanib[b] N=152**	***RET*-mutant MTC any-line population N=295**
Duration of overall survival (months)			
Median	[redacted]	64.3c	[redacted]
95% CI	[redacted]	48.3, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of overall survival			
≥12 months (95% CI)	[redacted]	87.8 (81.3, 92.1)	[redacted]
≥24 months (95% CI)	[redacted]	76.6 (68.8, 82.7)	[redacted]
≥36 months (95% CI)	[redacted]	67.8 (59.4, 74.8)	[redacted]
Duration of follow-up (months)			
Median	[redacted]	46.9	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Survival status (n, %)			
Dead	[redacted]	[redacted]	[redacted]
Censored	[redacted]	96 (63.2)	224 (75.9)

Based on Table 23 in the CS[5] and Table 12 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both cabozantinib and vandetanib
[c] Due to the median duration of follow-up for OS, median OS in the prior cabozantinib/vandetanib *RET*-mutant population is not considered meaningful and is expected to increase with increased follow up
'*' denotes where some data have been censored.
CI = confidence interval; CS = company submission; MTC = medullary thyroid cancer; NE = not estimable; NR = not reported; OS = overall survival; PD = progressed disease; *RET* = rearranged during transfection

KM plots of OS for the prior cabozantinib/vandetanib and the any-line *RET*-mutant MTC populations are shown in figures 3.11 and 3.12, respectively.

Figure 3.11: KM plot of OS in the prior cabozantinib/vandetanib *RET*-mutant MTC population



Based on Figure 15 in the CS[5]
KM = Kaplan-Meier; MTC = medullary thyroid cancer; No. = number of patients; OS = overall survival; *RET* = rearranged during transfection

Figure 3.12: KM plot of OS in any-line patients with *RET*-mutant MTC

[redacted]

Based on Figure 16 in the CS[5]
CI = confidence interval; KM = Kaplan-Meier; MTC = medullary thyroid cancer; NE = not estimable; OS = overall survival; *RET* = rearranged during transfection

3.2.5.3.2 RET fusion-positive thyroid cancer

OS results for the prior systemic therapy, prior Lenvatinib **or** sorafenib and the any-line *RET* fusion-positive TC populations are presented in Table 3.19.

The rate of OS for the prior systemic therapy *RET* fusion-positive TC population ranged from 94.8% (95% CI: 80.7%, 98.7%) at ≥12 months to 65.5% (95% CI: 46.0%, 79.4%) at ≥36 months.[5] The rate of OS for the prior lenvatinib **or** sorafenib *RET* fusion-positive TC population ranged from [redacted] at ≥12 months to [redacted] at ≥36 months.[1] After a median follow-up of [redacted], median OS was [redacted] for any of the three populations.

The CS states that: *"OS results were similar in the any-line RET fusion-positive TC patient population compared to the prior systemic therapy RET fusion-positive population, with median OS* [redacted] *and slightly higher landmark rates of OS at later timepoints."*[5]

EAG comment: The EAG notes that, at the DCO, 53/65 (81.5%) of patients in the any-line *RET* fusion-positive TC population were alive or lost to follow-up, compared to 30/41 (73.2%) of patients in the prior systemic therapy *RET* fusion-positive TC population and [redacted] of patients in the prior lenvatinib **or** sorafenib *RET* fusion-positive TC population. The EAG further notes that the rates of OS were between [redacted] in the prior lenvatinib **or** sorafenib *RET* fusion-positive TC population than in the prior systemic therapy *RET* fusion-positive TC, for all points recorded (≥12 months, ≥24 months and ≥36 months). The EAG therefore questions whether the OS results can be described as broadly consistent across populations with differing prior treatments.

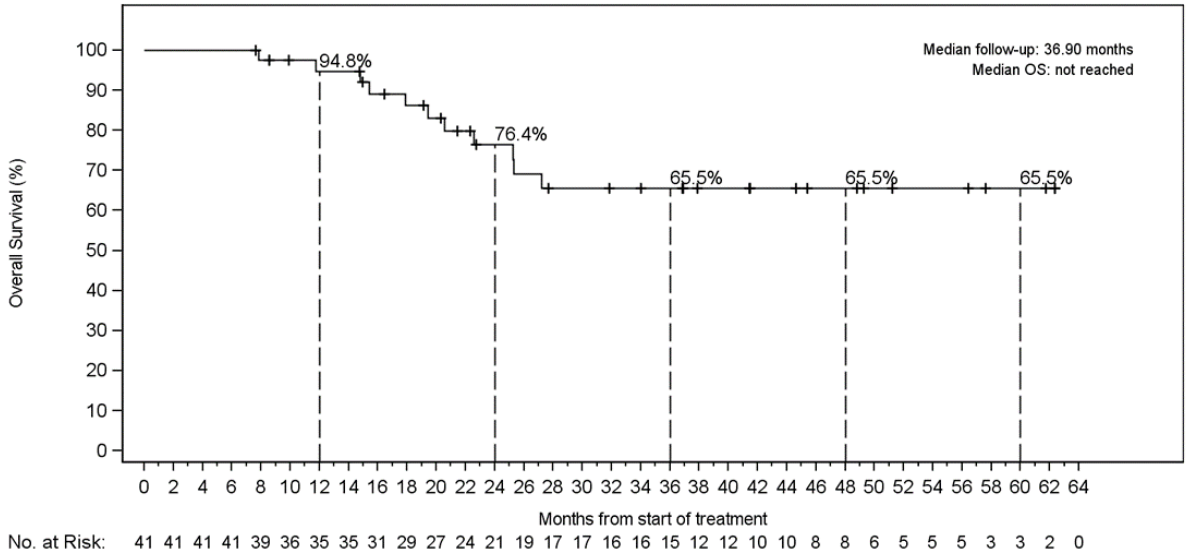
Table 3.20: OS for the patients with *RET* fusion-positive TC in the LIBRETTO-001 study

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib[a]** [redacted]	***RET* fusion-positive TC prior systemic therapy[b] N=41**	***RET* fusion-positive TC any-line population N=65**
Duration of OS (months)			
Median	[redacted]	NE	[redacted]
95% CI	[redacted]	25.3, NE	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]
Rate (%) of OS			
≥12 months (95% CI)	[redacted]	94.8 (80.7, 98.7)	[redacted]
≥24 months (95% CI)	[redacted]	76.4 (58.1, 87.5)	[redacted]
≥36 months (95% CI)	[redacted]	65.5 (46.0, 79.4)	[redacted]
Duration of follow-up (months)			
Median	[redacted]	36.9	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]
Survival status (n, %)			
Dead	[redacted]	[redacted]	[redacted]
Censored	[redacted]	30 (73.2)	53 (81.5)

Based on Table 29 in the CS[5] and Table 16 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both lenvatinib and sorafenib, and patients treated with other systemic therapies
'*' denotes where some data have been censored
CI = confidence interval; CS = company submission; NE = not estimable; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

Kaplan-Meier plots of OS for the prior systemic therapy and the any-line *RET*-fusion positive TC populations are shown in Figures 3.13 and 3.14, respectively.

Figure 3.13: KM plot of OS for the prior systemic therapy *RET* fusion-positive TC population



Based on Figure 23 in the CS[5]
CS = company submission; KM = Kaplan-Meier; No. = number of patients; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 3.14: KM plot of OS for any-line patients with *RET* fusion-positive TC

[redacted]

Based on Figure 24 in the CS[5]
CS = company submission; KM = Kaplan-Meier; No. = number of patients; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

3.2.5.4 Secondary outcome, included in the NICE scope, EORTC-QLQ-C30 (HRQoL)

3.2.5.4.1 RET-mutant medullary thyroid cancer

At data cut of the 13 January 2023, EORTC-QLQ-C30 data were available for [redacted] patients with prior cabozantinib/vandetanib *RET*-mutated MTC. Eligible patients had a mean baseline Global Health Status/QoL subscale score of [redacted] (SD=[redacted]). Mean baseline scores on the physical, emotional, cognitive, and social functioning subscales were all greater than [redacted]. Of the [redacted]. eligible patients, [redacted] showed a definite improvement in Global health status/QoL subscales on Day 1 of Treatment Cycle 3. On Day 1 of Treatment Cycle 9, [redacted] of patients did improve. The symptom subscales of the EORTC-QLQ-C30 showed clear improvements in the diarrhoea ([redacted]) and fatigue ([redacted]) subscales in a significant proportion of patients. The highest number of patients completed the questionnaire at weeks 3, 5, 7 and 9.[5]

EAG comment: The company only reported HRQoL data for patients with prior cabozantinib/vandetanib *RET*-mutated MTC, and not for any-line *RET*-mutated MTC population; all other clinical effectiveness results were provided for both populations and no explanation for the absence of data for any-line *RET*-mutated MTC population. HRQoL results were also omitted from the subgroup analyses, for the prior cabozantinib or vandetanib *RET*-mutated MTC population, provided by the company in response to clarification questions. The EAG notes that the provision of HRQoL data for the prior cabozantinib/vandetanib *RET*-mutated MTC population only means that it is not possible to assess whether HRQoL results were consistent across populations.

Table 3.21: Baseline scores of the symptom subscales of the EORTC-QLQ-C30, and proportion of patients showing improvement/worsening, in the prior cabozantinib/vandetanib *RET*-mutant MTC population at Day 1 of Cycle 9

Subscale	Prior cabozantinib/vandetanib *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]

Based on Tables 24 in the CS,[5]
[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).
CS = company submission; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30MTC = medullary thyroid cancer; *RET* = rearranged during transfection; SD = standard deviation.

Table 3.22: Proportion of patients with *RET*-mutant MTC who had received prior cabozantinib/vandetanib with improved or worsened EORTC-QLQ-C30 compared with baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		Prior cabozantinib/vandetanib *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]

QLQ-C30 Subscale, n (%)		Prior cabozantinib/vandetanib *RET*-mutant MTC ([redacted])[a]			
		Cycle 3	Cycle 5	Cycle 7	Cycle 9
	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]

Based on Tables 25 in the CS.[5]
The proportion of patients with no change, reported as "stable", are not included in this table.
[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).
CS = company submission; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MTC = medullary thyroid cancer; QoL = quality of life; *RET* = rearranged during transfection.

3.2.5.4.2 RET fusion-positive thyroid cancer

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

The mean baseline score on the eligible Global Health Status/QoL subscale among patients with *RET* fusion-positive TC who had received prior systemic therapy was [redacted] (SD=[redacted]). Mean baseline scores on the physical, emotional, cognitive, social, and role functioning subscales were greater than [redacted]. Of the [redacted] eligible patients, [redacted] showed a definite improvement in overall health status/QoL subscale on day 1 of treatment cycle 3. On Day 1 of Cycle 9, [redacted] of patients showed definite improvement.[5]

EAG comment: The company only reported HRQoL data for patients with prior systemic therapy *RET* fusion-positive TC, and not for any-line *RET* fusion-positive TC; all other clinical effectiveness results were provided for both populations and no explanation for the absence of data for any-line *RET* fusion-positive TC. HRQoL results were also omitted from the subgroup analyses, for the prior lenvatinib or sorafenib *RET* fusion-positive TC, provided by the company in response to clarification questions. The EAG notes that the provision of HRQoL data for the prior systemic therapy *RET* fusion-positive TC only means that it is not possible to assess whether HRQoL results were consistent across populations.

Table 3.23: Baseline scores of the symptom subscales of the EORTC-QLQ-C30, and proportion showing improvement/worsening, for patients in the prior systemic therapy *RET* fusion-positive TC population at Day 1 of Cycle 9

Subscale	Prior systemic therapy *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]

Based on Tables 30 in the CS,[5]
[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).
CS = company submission; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; *RET* = rearranged during transfection; SD = standard deviation; TC = thyroid cancer

Table 3.24: Proportion of patients in the prior systemic therapy *RET* fusion-positive TC population with improved or worsened EORTC-QLQ-C30 compared with baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		Prior systemic therapy *RET* fusion-positive TC ([redacted])[a]			
		Cycle 3	Cycle 5	Cycle 7	Cycle 9
	n	[redacted]	[redacted]	[redacted]	[redacted]

Global Health Status/QoL	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]
	n	[redacted]	[redacted]	[redacted]	[redacted]

Financial difficulties	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables 31 in the CS,[5]
The proportion of patients with no change, reported as "stable", are not included in this table.
[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)
CS = company submission; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL = quality of life; *RET* = rearranged during transfection; TC = thyroid cancer

3.2.5.5 Additional secondary outcome, not listed in the NICE scope, DOR

Duration of response 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.[5]

3.2.5.5.1 RET-mutant medullary thyroid cancer

Duration of response results for the prior cabozantinib/vandetanib, prior cabozantinib or vandetanib and the any-line *RET*-mutant MTC populations are presented in Table 3.25.

After a median follow-up of 38.3 months, the median DOR by IRC was 45.3 months (95% CI: 33.6, NE) for the prior cabozantinib/vandetanib *RET*-mutant MTC population[5] and [redacted] months [redacted] for the prior cabozantinib **or** vandetanib *RET*-mutant MTC population.[1] After a median follow-up of [redacted] months, the median DOR was [redacted] in the *RET*-mutant MTC any-line population.[5] Durable response rates in the prior cabozantinib **or** vandetanib *RET*-mutant MTC population were also observed; [redacted] of patients were in response for ≥12 months, reaching [redacted] at ≥36 months.

The CS states that: *"DOR results for the any-line MTC population were broadly consistent with the prior cabozantinib/vandetanib RET-mutant MTC population."*[5]

EAG comment: The EAG notes that the proportions of patients in response for ≥12 months, ≥24 months, and ≥36 months, were consistently [redacted] in the *RET*-mutant MTC any-line population than in the prior cabozantinib/vandetanib population, with differences between [redacted], [redacted] and [redacted], or in the prior cabozantinib or vandetanib population, with differences of [redacted], [redacted] and [redacted], for ≥12, ≥24 and ≥36 months, respectively. The EAG therefore questions whether the DOR results can be described as broadly consistent across populations with differing prior treatments.

Table 3.25: DOR based on IRC assessment for the prior cabozantinib/vandetanib MTC and the any-line *RET*-mutant MTC populations in the LIBRETTO-001 study

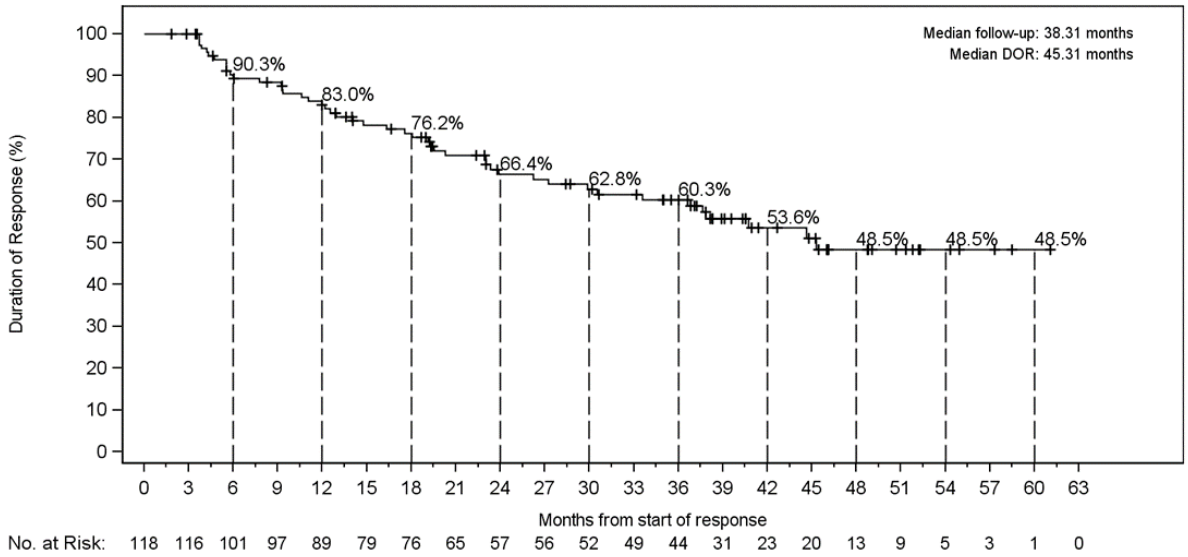
	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib[a]** [redacted]	***RET*-mutant MTC prior cabozantinib/vandetanib[b] N=152**	***RET*-mutant MTC any-line population N=295**
Responders (n)	[redacted]	118	236

	***RET*-mutant MTC prior treatment with cabozantinib or vandetanib[a]** [redacted]	***RET*-mutant MTC prior cabozantinib/vandetanib[b] N=152**	***RET*-mutant MTC any-line population N=295**
Reason censored (n, %)			
Alive without documented PD	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]
DOR (months)			
Median	[redacted]	45.3	[redacted]
95% CI	[redacted]	33.6, NE	[redacted]
Rate (%) of DOR			
≥12 months (95% CI)	[redacted]	83.0 (74.6, 88.8)	[redacted]
≥24 months (95% CI)	[redacted]	66.4 (56.3, 74.7)	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]
DOR follow-up (months)			
Median	[redacted]	38.3	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	23.0, 46.1	[redacted]

Based on Table 21 in the CS[5] and Table 10 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both cabozantinib and vandetanib
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

A KM plot of DOR for the prior cabozantinib/vandetanib *RET*-mutant MTC population is presented in Figure 3.15. No corresponding plot, for the any-line *RET*-mutant MTC population, was provided.

Figure 3.15: KM plot of DOR based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population



Based on Figure 12 in the CS[5]
CS = company submission; DOR = duration of response; IRC = independent review committee; KM = Kaplan-Meier; MTC = medullary thyroid cancer; No. = number of patients; *RET* = rearranged during transfection

3.2.5.5.2 RET fusion-positive thyroid cancer

Duration of response results for the prior systemic therapy, prior lenvatinib or sorafenib, and the any-line *RET*-fusion positive TC populations are presented in Table 3.26.

For the prior systemic therapy *RET* fusion-positive TC population, after a median follow-up of 33.9 months, the median DOR by IRC was 26.7 months (95% CI: 12.1, NE),[5] and for the prior lenvatinib **or** sorafenib *RET* fusion-positive TC population, after a median follow-up of [redacted] months, the median DOR by IRC was [redacted] months [redacted].[1] After a median follow-up of [redacted] months, the median DOR was [redacted] in the *RET*-mutant MTC any-line population.[5] Durable response rates in the prior lenvatinib **or** sorafenib *RET* fusion-positive TC population were observed with [redacted] of patients in response for ≥12 months and [redacted] at ≥36 months.[1]

The CS states that: *"DOR results for the prior systemic therapy RET fusion-positive population were broadly consistent with the any-line TC population, with DOR landmark rates for the any-line RET fusion-positive TC population being slightly higher than the prior systemic therapy RET fusion-positive TC population. Additionally, median DOR was [redacted] (95% CI: [redacted]) in the any line population."*[5]

EAG comment: The EAG notes that the proportions of patients in response for ≥12 months, ≥24 months, and ≥36 months, were consistently [redacted] in the *RET* fusion-positive any-line population than in the prior lenvatinib **or** sorafenib population, with a difference of between [redacted] and [redacted]. The EAG therefore questions whether the DOR results can be described as broadly consistent across populations with differing prior treatments.

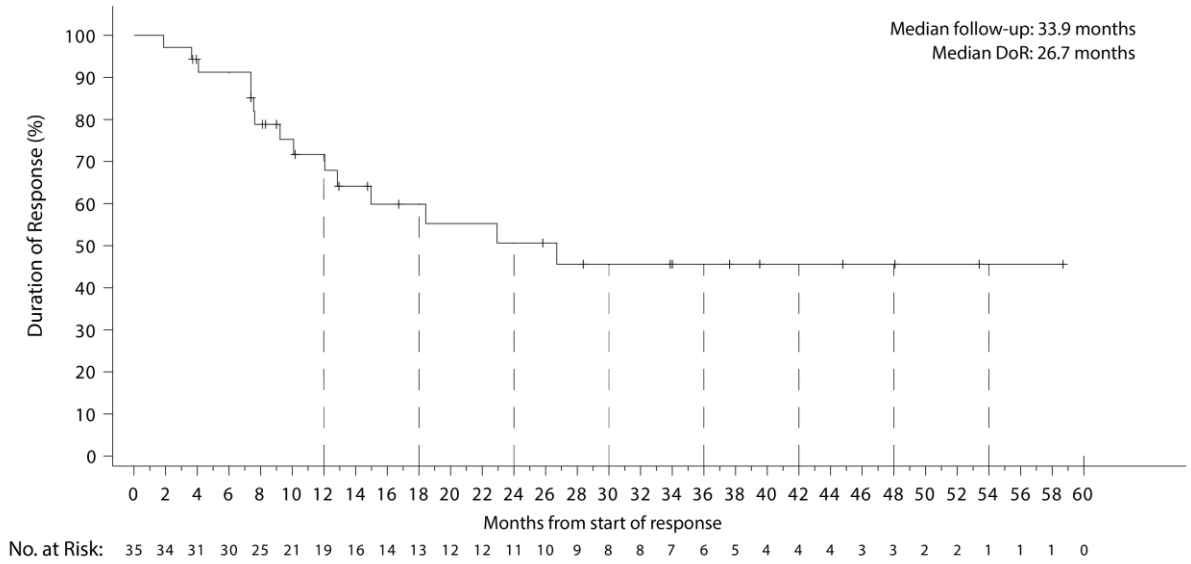
Table 3.26: DOR based on IRC assessment for patients with *RET* fusion-positive TC in the LIBRETTO-001 study

	***RET* fusion-positive TC prior treatment with lenvatinib or sorafenib[a]** [redacted]	***RET* fusion-positive TC prior systemic therapy[b] N=41**	***RET* fusion-positive TC any-line population N=65**
Responders (n)	[redacted]	35	58
Reason censored (n, %)			
Alive without documented PD	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]
DOR (months)			
Median	[redacted]	26.7	[redacted]
95% CI	[redacted]	12.1, NE	[redacted]
Rate (%) of DOR			
≥12 months (95% CI)	[redacted]	71.7 (52.4, 84.2)	[redacted]
≥24 months (95% CI)	[redacted]	50.7 (30.4, 67.8)	[redacted]
≥36 months (95% CI)	[redacted]	45.6 (25.6, 63.6)	[redacted]
DOR follow-up (months)			
Median	[redacted]	33.9	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	12.9, 44.8	[redacted]

Based on Table 27 in the CS[5] and Table 14 in the response to clarification questions[1]
[a] Population in-line with the decision problem
[b] Including patients who had previously received both lenvatinib and sorafenib, and patients treated with other systemic therapies
CI = confidence interval; CS = company submission; DOR = duration of response; IRC = independent review committee; N = number of patients; NE = not estimable; NR = not reported; PD: disease progression; *RET* = rearranged during transfection; TC = thyroid cancer

Kaplan-Meier plots of DOR for the prior systemic therapy and the any-line *RET*-fusion positive TC populations are shown in Figures 3.16 and 3.17, respectively.

Figure 3.16: KM plot of DOR based on IRC assessment for the prior systemic therapy *RET*-fusion positive TC population



Based on Figure 19 in the CS[5]
CS = company submission; DOR = duration of response; IRC = independent review committee; KM = Kaplan-Meier; No. = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 3.17: KM plot of DOR based on IRC assessment for any-line patients with *RET*-fusion positive TC

[redacted]

Based on Figure 20 in the CS[5]
CS = company submission; DOR = duration of response; IRC = independent review committee; KM = Kaplan-Meier; No. = number of patients; *RET* = rearranged during transfection; TC = thyroid cancer

3.2.6 Subgroup analyses from the LIBRETTO-001 study

The NICE scope[3] listed the following subgroups of interest:

- Type of thyroid cancer within advanced *RET* fusion-positive thyroid cancer (such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma).
- Specific type of *RET* alteration (within *RET* fusion-positive thyroid cancer or *RET*-mutation positive MTC) may need to be considered, as some types of *RET* genetic alteration may be more or less sensitive to selpercatinib.

The CS included some subgroup analyses, for these and additional subgroups, for ORR and DOR, and in the prior cabozantinib/vandetanib *RET*-mutant MTC and prior systemic therapy *RET* fusion-positive

TC populations only. No subgroup analyses were presented for either the any-line *RET*-mutant MTC or the any-line *RET* fusion-positive TC populations.[5]

EAG comment: Noting that no subgroup analyses were presented for the populations and outcomes used in the cost-effectiveness modelling, at clarification, the EAG requested provision of data for all listed subgroups and for all outcomes available and for all populations used in the submission; additional subgroup data provided are summarised in this section of the EAG report.[1]

3.2.6.1 RET-mutant medullary thyroid cancer

Subgroup data, for the subgroups specified in the NICE scope (type of *RET* alteration), for ORR and DOR in the prior cabozantinib/vandetanib *RET*-mutant MTC population are presented in Table 3.27. Subgroup data by prior systemic therapy have also been included, as these data may be considered relevant to one of the areas of uncertainty specified in the managed access agreement for selpercatinib for treating advanced thyroid cancer with *RET* alterations: *"Generalisability of data from the LIBRETTO-001 study to UK clinical practice in terms of prior treatment."*[15]

The CS states that: *"ORR was broadly consistent for patients with different RET mutations. However, in patients with a V804M or V804L mutation, ORR was slightly higher. Median DOR was* [redacted] *in some subgroups, whilst in the remaining subgroups, median DOR was broadly consistent with the overall population."*[5]

EAG comment: Clinical expert opinion (sought by the EAG, Appendix 1) has indicated that UK treatment pathway for the *RET*-mutant MTC population is cabozantinib (with vandetanib generally only used where cabozantinib is not tolerated), followed by selpercatinib or BSC; i.e., cabozantinib and vandetanib are not routinely used sequentially in UK clinical practice. The EAG notes that prior treatment with both cabozantinib and vandetanib occurred in [redacted]152 [redacted] of prior cabozantinib/vandetanib *RET*-mutant MTC population in the LIBRETTO-001 study and appeared to be associated with a [redacted] ORR than prior treatment with either cabozantinib or vandetanib alone.

The EAG notes that, in response to clarification questions, additional subgroup data were provided for response outcomes by *RET* mutation, in the any-line *RET*-mutant MTC population;[1] these data did not differ substantively from those presented below (Table 3.27), for the prior cabozantinib/vandetanib *RET*-mutant MTC population. Most patients, in both the prior cabozantinib/vandetanib *RET*-mutant MTC and any-line *RET*-mutant MTC populations had M918T mutations; whilst there appears to be some variation in response outcomes for people with different mutations, differences are generally small and the numbers of patients with mutations other than M918T were too small to support meaningful comparisons.

Table 3.27: ORR and DOR by *RET* mutation and by prior systemic therapy, based on IRC assessment, for the prior cabozantinib/vandetanib *RET*-mutant MTC population

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
Overall	152	118	77.6 (70.2, 84.0)	45.3 (33.6, NE)
***RET* mutation type**				
M918T	99	[redacted]	[redacted]	[redacted]
Extracellular Cysteine Mutation	24	[redacted]	[redacted]	[redacted]

Baseline characteristic	N	Responders	ORR, % (95% CI)	DOR, months (range)
V804M/L[a]	8	[redacted]	[redacted]	[redacted]
Other	21	[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]
Number of prior therapies				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Type of prior systemic therapy				
Prior MKI of cabozantinib only	[redacted]	[redacted]	[redacted]	[redacted]
Prior MKI of vandetanib only	[redacted]	[redacted]	[redacted]	[redacted]
Prior MKI of both cabozantinib and vandetanib	[redacted]	[redacted]	[redacted]	[redacted]
Prior MKI other than cabozantinib or vandetanib	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapies other than MKI	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables 33 and 34 in the CS,[5] and Table 14.2.7.1, page 852 in the CSR[14]
[a] Patient has either V804M or V804L mutation
CS = company submission; DOR = duration of response; FISH = fluorescence in situ hybridisation; IRC = independent review committee; MKI = multikinase inhibitor; MTC = medullary thyroid cancer; NA = not applicable; NE = not estimable; NGS = next generation sequencing; NR = not reported; ORR = objective response rate; PCR = polymerase chain reaction; *RET* = rearranged during transfection

Objective response rate subgroup analyses for the prior cabozantinib/vandetanib *RET*-mutant MTC population are summarised in Figure 3.18.

In response to clarification questions, the company also provided subgroup analyses for survival outcomes (OS and PFS), by *RET* mutation only, in both the any-line and prior cabozantinib/vandetanib *RET*-mutant MTC populations.[1] The results of these analyses are reproduced, in full, in Tables 3.28 to 3.31.

Figure 3.18: Forest plot of ORR in subgroup populations based on IRC assessment for the prior cabozantinib/vandetanib *RET*-mutant MTC population

Based on Figure 25 in the CS[5]
CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; MKI = multikinase inhibitor; MTC = medullary thyroid cancer; NGS = next generation sequencing; ORR = overall response rate; PCR = polymerase chain reaction; *RET* = rearranged during transfection

Table 3.28: PFS based on IRC assessment by *RET* mutation within the prior cabozantinib/vandetanib *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/L[a] N=8	Other N=21
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related	[redacted]	[redacted]	[redacted]	[redacted]

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/L[a] N=8	Other N=21
surgery without documented PD				
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 29 in the response to clarification questions[1]
'*' denotes where some data have been censored
[a] Patient has either V804M or V804L mutation
CI = confidence interval; IRC = independent review committee; MTC = medullary thyroid cancer; NE = not estimable; PD = disease progression; PFS = progression-free survival; *RET* = rearranged during transfection

Table 3.29: PFS based on IRC assessment by *RET* mutation within the any-line *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/L[a] N=14	Other N=38
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 30 in the response to clarification questions[1]
'*' denotes where some data have been censored
[a] Patient has either V804M or V804L mutation
CI = confidence interval; IRC = independent review committee; MTC = medullary thyroid cancer; NE = not estimable; NR = not reported; PD = disease progression; PFS = progression-free survival; *RET* = rearranged during transfection

Table 3.30: OS by *RET* mutation within the prior cabozantinib/vandetanib *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=24	M918T N=99	V804M/L[a] N=8	Other N=21
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 31, response to clarification questions[1]
'*' denotes where some data have been censored
[a] Patient has either V804M or V804L mutation
CI = confidence interval; MTC = medullary thyroid cancer; NE = not estimable; OS = overall survival; *RET* = rearranged during transfection

Table 3.31: OS by *RET* mutation within the any-line *RET*-mutant MTC population

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/L[a] N=14	Other N=38
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

	Extracellular Cysteine Mutation N=58	M918T N=185	V804M/L[a] N=14	Other N=38
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 32 in the response to clarification questions[1]
'*' denotes where some data have been censored
[a] Patient has either V804M or V804L mutation
CI = confidence interval; MTC = medullary thyroid cancer; NE = not estimable; OS = overall survival; *RET* = rearranged during transfection

The EAG notes that most patients, in both the prior cabozantinib/vandetanib *RET*-mutant MTC and any-line *RET*-mutant MTC populations had M918T mutations; whilst there appears to be some variation in survival outcomes for people with different mutations, differences are generally small and the numbers of patients with mutations other than M918T were too small to support meaningful comparisons.

3.2.6.2 RET fusion-positive thyroid cancer

Subgroup data, for the subgroups specified in the NICE scope (type of *RET* alteration and type of thyroid cancer), for ORR and DOR in the prior systemic therapy *RET* fusion-positive TC population are presented in Table 3.32. Subgroup data by prior systemic therapy have also been included, as these data may be considered relevant one of the areas of uncertainty specified in the managed access agreement for selpercatinib for treating advanced thyroid cancer with *RET* alterations: *"Generalisability of data from the LIBRETTO-001 study to UK clinical practice in terms of prior treatment."*[15]

The CS states that: *"ORR was broadly consistent across the number of prior therapies. DOR was* [redacted] *for the two prior therapies subgroup (*[redacted]*). There was some variation across the other prior therapies subgroups, which may be due to the small patient numbers associated with these subgroups."*[5]

EAG comment: Clinical expert opinion (sought by the EAG, Appendix 1) has indicated that the UK treatment pathway for the *RET* fusion-positive TC population is lenvatinib (with sorafenib generally only used where lenvatinib is not tolerated), followed by selpercatinib or BSC; i.e., lenvatinib and sorafenib are not routinely used sequentially in UK clinical practice. The EAG notes that small number of patients in the prior systemic therapy *RET* fusion-positive TC population in the LIBRETTO-001 study had previously been treated with both lenvatinib and sorafenib (4 [9.8%]), which may be considered reflective of UK clinical practice.

The EAG notes that, in response to clarification questions, additional subgroup data were provided for response outcomes by *RET* mutation, in the any-line *RET* fusion-positive TC population;[1] these data did not differ substantively from those presented below (Table 3.32), for the prior systemic therapy *RET* fusion-positive TC population. Most patients, in both the prior systemic therapy *RET* fusion-positive

TC and any-line *RET* fusion-positive TC populations had CCDC6 fusions; the numbers of patients with fusions other than CCDC6 were too small to support meaningful comparisons between different fusions.

The EAG notes that, in response to clarification questions, additional subgroup data were provided for response outcomes by type of TC, in the any-line *RET* fusion-positive TC population;[1] these data did not differ substantively from those presented below (Table 3.32), for the prior systemic therapy *RET* fusion-positive TC population. Most patients, in both the prior systemic therapy *RET* fusion-positive TC and any-line *RET* fusion-positive TC populations had PTC; the numbers of patients with other types of TC were too small to support meaningful comparisons between different histological cancer types. However, it should be noted that (within the small numbers of patients, prior systemic therapy *RET* fusion-positive TC population, with cancer types other than PTC) ORRs were generally high; [redacted]/4 patients with ATC, and [redacted] patients with Hürthle cell TC (n=1) or poorly differentiated TC (n=5).

Table 3.32: ORR and DOR by *RET* fusion, type of thyroid cancer and prior systemic therapy, based on IRC assessment, for the prior systemic therapy *RET* fusion-positive TC population

Baseline characteristic	N	Responders	ORR[a], % (95% CI)	Median DOR, months (range)
Overall	41	35	85.4 (70.8, 94.4)	[redacted]
***RET* mutation type**				
CCDC6	25	[redacted]	[redacted]	[redacted]
NCOA4	8	[redacted]	[redacted]	[redacted]
Other	7	[redacted]	[redacted]	[redacted]
C10ORF118	[redacted]	[redacted]	[redacted]	[redacted]
ERC1	[redacted]	[redacted]	[redacted]	[redacted]
GOLGA5	[redacted]	[redacted]	[redacted]	[redacted]
KTN1	[redacted]	[redacted]	[redacted]	[redacted]
RUFY3	[redacted]	[redacted]	[redacted]	[redacted]
SPECC1L	[redacted]	[redacted]	[redacted]	[redacted]
TRIM24	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	1	[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]
Number of prior systemic therapies				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristic	N	Responders	ORR[a], % (95% CI)	Median DOR, months (range)
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Prior MKI				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Tumour subtype per histology				
Anaplastic thyroid cancer	4	[redacted]	[redacted]	[redacted]
Hürthle cell thyroid cancer	1	[redacted]	[redacted]	[redacted]
Papillary thyroid cancer	31	[redacted]	[redacted]	[redacted]
Poorly differentiated thyroid cancer	5	[redacted]	[redacted]	[redacted]

Based on Tables 36 and 37 in the CS,[5] and Table 14.2.7.1, pages 906-907 in the CSR[14]
[a] Percentage ORR is not calculated when number of patients is ≤2, best overall response is shown instead.
CI = confidence interval; CR = complete response; CS = company submission; CSR = Clinical Study Report; DOR = duration of response; FISH = fluorescence in situ hybridisation; IRC = independent review committee; MKI = multikinase inhibitor; NA = not applicable; NE = not estimable; NGS = next generation sequencing; ORR = objective response rate; PR = partial response; *RET* = rearranged during transfection; SD = stable disease; TC = thyroid cancer

All ORR subgroup analyses performed for the prior systemic therapy *RET* fusion-positive TC population are summarised in Figure 3.19.

Figure 3.19: Forest plot of ORR in subgroup populations based on IRC assessment for the prior systemic therapy RET fusion-positive TC population

Based on Figure 26 in the CS[5]
CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; IRC = independent review committee; NGS = next generation sequencing; ORR = overall response rate; *RET* = rearranged during transfection; TC = thyroid cancer

In response to clarification questions, the company also provided subgroup analyses for survival outcomes (OS and PFS), by *RET* mutation and by histological type of TC, in both the any-line and prior systemic therapy *RET* fusion-positive TC populations.[1] Given the very small numbers of patients with cancer types other than PTC or fusions other than CCDC6, only the results of these analyses for the any-line population have been included in this report (Tables 3.33 to 3.36).

Table 3.33: PFS based on IRC assessment by type of thyroid cancer within the any-line *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=54	Poorly DTC N=6
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 22 in the response to clarification questions[1]
'*' denotes where some data have been censored
ATC = anaplastic thyroid cancer; CI = confidence interval; DTC = differentiated thyroid cancer; IRC = independent review committee; NE = not estimable NR = not reported; PD = disease progression; PFS = progression-free survival; PTC = papillary thyroid cancer; *RET* = rearranged during transfection; TC = thyroid cancer

Table 3.34: OS by type of thyroid cancer within the any-line *RET* fusion-positive TC population

	ATC N=4	Hürthle Cell TC N=1	PTC N=54	Poorly DTC N=6
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 24 in the response to clarification questions[1]
'*' denotes where some data have been censored
ATC = anaplastic thyroid cancer; CI = confidence interval; DTC = differentiated thyroid cancer; NE = not estimable; NR = not reported; OS = overall survival; PTC = papillary thyroid cancer; *RET* = rearranged during transfection; TC = thyroid cancer

The EAG notes that most patients in the any-line *RET* fusion-positive TC population had PTC; the numbers of patients with other types of TC were too small to support meaningful comparisons between different histological cancer types.

Table 3.35: PFS based on IRC assessment by *RET* fusion within the any-line *RET* fusion-positive TC population

	CCDC6 N=40	NCOA4 N=15	Other N=9	Unknown N=1
Reason censored (n, %)				
Alive without documented disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]	[redacted]	[redacted]
Died or documented PD after missing two or more consecutive visits	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PFS (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of PFS				
≥12 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months or more (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Progression status (n, %)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 38 in the response to clarification questions[1]
'*' denotes where some data have been censored
CI = confidence interval; IRC = independent review committee; NE = not estimable; PD = disease progression; PFS = progression-free survival; *RET* = rearranged during transfection; TC = thyroid cancer

Table 3.36: OS by *RET* fusion within the any-line *RET* fusion-positive TC population

	CCDC6 N=40	NCOA4 N=15	Other N=9	Unknown N=1
Duration of overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of OS				
≥12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of follow-up (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Survival status (n, %)				
Dead	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 40 in the response to clarification questions[1]
'*' denotes where some data have been censored
CI = confidence interval; NE = not estimable; NR = not reported; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

EAG comment: The EAG notes that most patients in the any-line *RET* fusion-positive TC population had CCDC6 fusions; the numbers of patients with mutations other than CCDC6 were too small to support meaningful comparisons between different mutations.

3.2.7 Safety results of the LIBRETTO-001 study

The following section presents a summary of the safety data for the *RET*-mutant MTC, the *RET* fusion-positive TC and overall safety analysis set (OSAS) in LIBRETTO-001.

3.2.7.1 Treatment duration and dosage

Following Phase I dose escalation, the Phase II dose of selpercatinib was set at 160 mg BID, a regimen adhered to by the majority of patients in the LIBRETTO-001 trial. Most patients with *RET*-mutant MTC ([redacted]), *RET* fusion-positive TC ([redacted]), and in the OSAS ([redacted]) started at this dose. The OSAS provides safety data for all N=837 patients treated with at least one or more doses of selpercatinib, covering all *RET*-altered cancer types enrolled in LIBRETTO-001. The relative dose intensities were [redacted] for *RET*-mutant MTC, [redacted] for RET fusion-positive TC, and [redacted] for OSAS, with mean treatment durations of [redacted], [redacted], and [redacted] months, respectively. Adverse events led to dose reductions in [redacted] of *RET*-mutant MTC, [redacted]% of *RET* fusion-positive TC, and [redacted] of OSAS patients, and dose interruptions in [redacted], [redacted], and [redacted] of these groups, respectively.[5]

Table 3.37: Starting doses of selpercatinib

	RET-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
Starting dose, n (%)			
20 mg QD	[redacted]	[redacted]	[redacted]
20 mg BID	[redacted]	[redacted]	[redacted]
40 mg BID	[redacted]	[redacted]	[redacted]
60 mg BID	[redacted]	[redacted]	[redacted]
80 mg BID	[redacted]	[redacted]	[redacted]
120 mg BID	[redacted]	[redacted]	[redacted]
160 mg QD	[redacted]	[redacted]	[redacted]
160 mg BID	[redacted]	[redacted]	[redacted]
200 mg BID	[redacted]	[redacted]	[redacted]
240 mg BID	[redacted]	[redacted]	[redacted]

Based on Tables 44 in the CS,[5] and Table 25 in the Appendix F[11]
BID = twice daily; CS = company submission; MTC = medullary thyroid cancer; N = number of patients in safety analysis set; n = number of patients; OSAS = overall safety analysis set; QD = once daily; *RET* = rearranged during transfection; SAS = safety analysis set; TC = thyroid cancer

Table 3.38: Selpercatinib time on treatment and relative dose intensity

	RET-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
Time on treatment, months			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Relative dose intensity (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Category, n (%)			
≥90%	[redacted]	[redacted]	[redacted]
75–90%	[redacted]	[redacted]	[redacted]
50–75%	[redacted]	[redacted]	[redacted]
<50%	[redacted]	[redacted]	[redacted]

Based on Tables 45 in the CS,[5] and Table 26 in the Appendix F[11]
CS = company submission; MTC = medullary thyroid cancer; n = number of patients; OSAS = overall safety analysis set; RET = rearranged during transfection; SAS = safety analysis set; SD = standard deviation; TC = thyroid cancer

Table 3.39: Selpercatinib dose modifications

	RET-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
Dose reduction, n (%)			
Any	[redacted]	[redacted]	[redacted]

	RET-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
AE	[redacted]	[redacted]	[redacted]
Intra-patient dose escalation	[redacted]	[redacted]	[redacted]
For other reason	[redacted]	[redacted]	[redacted]
Dose withheld, n (%)			
Any	[redacted]	[redacted]	[redacted]
For AE	[redacted]	[redacted]	[redacted]
For other reason	[redacted]	[redacted]	[redacted]
Dose increase, n (%)			
Any	[redacted]	[redacted]	[redacted]
Intra-patient escalation[a]	[redacted]	[redacted]	[redacted]
Reescalation[b]	[redacted]	[redacted]	[redacted]
Other reason	[redacted]	[redacted]	[redacted]

Based on Tables 46 in the CS,[5] and Table 27 in the Appendix F[11]
[a] Started at a lower dose during dose escalation that was subsequently increased
[b] Reescalation after a dose reduction
AE = adverse event; CS = company submission; MTC = medullary thyroid cancer; n = number of patients; OSAS = overall safety analysis set; *RET* = rearranged during transfection; SAS = safety analysis set; TC = thyroid cancer

3.2.7.2 Summary of adverse events

In the LIBRETTO-001 trial, nearly all patients experienced treatment-emergent adverse events (TEAEs) related to selpercatinib, with severe TEAEs (Grade ≥3) occurring in 42.9% of *RET*-mutant MTC, 36.4% of *RET* fusion-positive TC, and [redacted] of OSAS patients. Treatment discontinuations due to TEAEs were notable, particularly in the *RET*-mutant MTC (9.3%) and OSAS ([redacted]) groups. Serious adverse events (TE-SAEs) related to selpercatinib occurred in 13.3% of RET-mutant MTC, in 4.5% of *RET* fusion-positive TC patients and in [redacted] of OSAS patients. Totally [redacted] deaths were reported with [redacted] death in the *RET*-mutant MTC SAS was attributed to selpercatinib treatment.[5]

Table 3.40: Summary of TEAEs in the LIBRETTO-001 trial

	RET-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
Any TEAE, n (%)			
All	324 (100.0)	66 (100.0)	[redacted]
Related to selpercatinib	310 (95.7)	65 (98.5)	[redacted]
Grade ≥3 TEAE, n (%)			
All	249 (76.9)	47 (71.2)	[redacted]
Related to selpercatinib	139 (42.9)	24 (36.4)	[redacted]
TEAE leading to permanent treatment discontinuation, n (%)			
All	30 (9.3)	2 (3.0)	[redacted]

	RET-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
Related to selpercatinib	17 (5.2)	1 (1.5)	[redacted]
TE-SAE, n (%)			
All	167 (51.5)	25 (37.9)	[redacted]
Related to selpercatinib	43 (13.3)	3 (4.5)	[redacted]
Fatal TEAE, n (%)			
All	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]

Based on Tables 47 in the CS,[5] and Table 28 in the Appendix F[11]
CS = company submission; MTC = medullary thyroid cancer; OSAS = overall safety analysis set; *RET* = rearranged during transfection; SAE = serious adverse event; SAS = safety analysis set; TC = thyroid cancer; TE = treatment emergent; TEAE = treatment-emergent adverse event

3.2.7.3 Common treatment-emergent adverse events

Table 3.41 provides an overview of TEAEs by grade (15% or greater of patients per analysis set) in patients with *RET*-mutant MTC, *RET* fusion-positive TC, and the OSAS. Across all groups, common AEs included oedema, diarrhoea, fatigue, hypertension, and aspartate aminotransferase (AST) increase. While the prevalence of certain AEs varied between groups, such as grade ≥3 hypertension being more common in *RET*-mutant MTC patients and diarrhoea in *RET* fusion-positive TC patients, others, e.g. rash,increase were consistent across all populations.[5]

Table 3.41: 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)		OSAS (N=837)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	22 (6.8)	36 (54.5)	5 (7.6)	[redacted]	49 (5.9)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	140 (43.2)	0 (0.0)	33 (50.0)	0 (0.0)	366 (43.7)	0 (0.0)
Hypertension	[redacted]	[redacted]	[redacted]	10 (15.2)	[redacted]	[redacted]
AST increase	118 (36.4)	25 (7.7)	16 (24.2)	[redacted]	316 (37.8)	73 (8.7)
Rash	[redacted]	[redacted]	[redacted]	0 (0.0)	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	3 (4.5)	[redacted]	[redacted]
ALT increase	107 (33.0)	29 (9.0)	[redacted]	[redacted]	305 (36.4)	99 (11.8)
Constipation	139 (42.9)	1 (0.3)	27 (40.9)	0 (0.0)	295 (35.2)	7 (0.8)
Nausea	127 (39.2)	5 (1.5)	20 (30.3)	0 (0.0)	289 (34.5)	14 (1.7)
Blood creatine increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	109 (33.6)	9 (2.8)	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	*RET*-mutant MTC SAS (N=324)		*RET* fusion-positive TC SAS (N=66)		OSAS (N=837)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cough	[redacted]	0 (0.0)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	94 (29.0)	8 (2.5)	24 (36.4)	2 (3.0)	226 (27.0)	20 (2.4)
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	19 (28.8)	1 (1.5)	192 (22.9)	3 (0.4)
Back pain	[redacted]	[redacted]	17 (25.8)	2 (3.0)	187 (22.3)	17 (2.0)
Decreased appetite	[redacted]	[redacted]	19 (28.8)	1 (1.5)	185 (22.1)	7 (0.8)
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolongation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	92 (28.4)	17 (5.2)	[redacted]	[redacted]	142 (17.0)	24 (2.9)
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables 48 in the CS,[5] and Table 29 in the Appendix F[11]
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission; ECG = electrocardiogram; MTC = medullary thyroid cancer; N = number of patients in the population; n = number of patients per category; OSAS = overall safety analysis set; *RET* = rearranged during transfection; SAS = safety analysis set; TC = thyroid cancer; TEAE = treatment-emergent adverse event

3.2.7.4 Grade 3–4 adverse events

Grade 3–4 TEAEs were observed in a substantial proportion of patients across analysis sets, with [redacted] in the *RET*-mutant MTC SAS, [redacted] in the *RET* fusion-positive TC SAS, and [redacted] in the OSAS. Notable Grade 3–4 TEAEs included hypertension, affecting [redacted], 15.2%, and [redacted] of patients in the respective analysis sets, and ALT increase, observed in 9.0%, [redacted] and [redacted] of patients, respectively. Additionally, diverse Grade 3–4 TEAEs were noted, such as hyponatremia, AST increase and diarrhoea.[5]

Table 3.42: Grade 3–4 TEAEs in 2% or more patients

Preferred term	*RET*-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
Patients with TEAEs	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	10 (15.2)	[redacted]
ALT increase	29 (9.0)	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]
AST increase	25 (7.7)	[redacted]	73 (8.7)
Diarrhoea	22 (6.8)	5 (7.6)	49 (5.9)
Lymphopenia	[redacted]	[redacted]	[redacted]

Preferred term	*RET*-mutant MTC SAS (N=324)	*RET* fusion-positive TC SAS (N=66)	OSAS (N=837)
ECG QT prolongation	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	29 (3.5)
Anaemia	[redacted]	[redacted]	[redacted]
Abdominal pain	10 (3.1)	3 (4.5)	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]
Hypocalcaemia	17 (5.2)	[redacted]	24 (2.9)
Pleural effusion	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increase	[redacted]	[redacted]	[redacted]
Blood creatinine increase	[redacted]	[redacted]	[redacted]
Vomiting	8 (2.5)	2 (3.0)	20 (2.4)
Weight increase	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]

Based on Tables 49 in the CS,[5] and Table 30 in the Appendix F[11]
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission; ECG = electrocardiogram; MTC = medullary thyroid cancer; n = number of patients; OSAS = overall safety analysis set; *RET* = rearranged during transfection; SAS = safety analysis set; TC = thyroid cancer; TEAE = treatment emergent adverse event

3.2.7.5 Adverse events of special interest

In the LIBRETTO-001 trial, five adverse events of special interest (AESIs) were reported: AST increase, alanine aminotransferase (ALT) increase, hypertension, drug hypersensitivity, and QT prolongation. In the *RET*-mutant MTC SAS, 36.4% experienced AST increases, 33.0% had ALT increases, and [redacted]% reported hypertension, with related Grade 3 events at [redacted]%, [redacted]%, and [redacted]%, respectively. Comparatively, the *RET* fusion-positive TC SAS showed lower incidences of AST ([redacted]%) and ALT ([redacted]%) increases, but similar rates of hypertension ([redacted]%). The OSAS group exhibited slightly higher incidences for AST ([redacted]%) and ALT ([redacted]%) increases, with hypertension affecting [redacted]% of patients. Notably, drug hypersensitivity was infrequent but more common in the OSAS group ([redacted]%). QT prolongation was observed in [redacted]% of *RET*-mutant MTC SAS patients and [redacted]% of *RET* fusion-positive TC SAS patients, with related cases at [redacted]% for both groups. These findings indicate that while selpercatinib is effective, it presents significant risks for liver enzyme elevations and hypertension, necessitating careful monitoring and management.[5]

Table 3.43: 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)			OSAS (N=837)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
AST increase, n (%)									
All	118 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increase									
All	107 (33.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension									
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity, n (%)									
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs deemed as an 'SAE' attributed to selpercatinib, n (%)	[redacted]			[redacted]			[redacted]		
Median time to first onset, weeks (range)	[redacted]			[redacted]			[redacted]		
AEs leading to dose withheld	[redacted]			[redacted]			[redacted]		
AEs leading to dose reduction	[redacted]			[redacted]			[redacted]		
AEs leading to dose discontinuation	[redacted]			[redacted]			[redacted]		
QT prolongation									
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Tables 50 and 51 in the CS,[5] and Table 31 and 32 in the Appendix F[11]

AE = adverse event; AESI = adverse event of special interest; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CS = company submission; MTC = medullary thyroid cancer; n = number of

Adverse event of special interest, n (%)	*RET*-mutant MTC SAS (N=324)			*RET* fusion-positive TC SAS (N=66)			OSAS (N=837)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
patients; OSAS = overall safety analysis set; *RET* = rearranged during transfection; SAE = serious adverse event; SAS = safety analysis set; TC = thyroid cancer									

EAG comment: The LIBRETTO-001 trial data highlights a high incidence of adverse events, with [redacted] patients experiencing at least one TEAEs and [redacted] of all patients experiencing at least one TEAE that was considered to be related to selpercatinib. Grade ≥3 TEAEs and TE-SAEs were also common, affecting more [redacted] and [redacted] of all patients, respectively. The EAG notes that the proportion of patients experiencing a grade ≥3 TEAE or a TE-SAE that was considered to be related to selpercatinib was [redacted] than that for any TEAE. Overall, [redacted] deaths were reported, with [redacted] in the *RET*-Mutant MTC SAS population and [redacted] in the *RET* fusion-positive SAS population; only [redacted] death in the *RET*-mutant MTC SAS was related to selpercatinib treatment and no cause-of-death information was provided for the other [redacted] patients.

3.2.8 Systemic Anti-Cancer Therapy (SACT) dataset

Following TA742,[4] selpercatinib was recommended for use within the CDF:

- For advanced *RET*-mutant MTC in people aged 12 years and older who require systemic therapy after cabozantinib or vandetanib
- For advanced *RET* fusion-positive TC in people aged 12 years and older who require systemic therapy after sorafenib or lenvatinib

NHS England have evaluated the real-world treatment effectiveness of selpercatinib in the CDF population, during the managed access period, using the routinely collected SACT dataset.[16] There were 24 applications for selpercatinib in the period 1 October 2021 to 31 March 2023; four patients were excluded (received selpercatinib prior to the CDF), one patient died before treatment and one further patient did not receive treatment (confirmed by the trust). All of the remaining 18 patients received selpercatinib as a treatment for *RET*-mutant MTC; there are no SACT data for patients with *RET* fusion-positive TC.

The majority of patients in the SACT dataset, 72% (n=13), were male. Most of the cohort 78% (n=14) were aged over 50 years and 67% (n=12) of patients had a performance status between 0 and 2 at the start of their selpercatinib regimen.

The median treatment duration was not reached; 94% (95% CI: 65%, 99%) of patients were still receiving treatment at 6 months, and 80% (95% CI: 35%, 95%) of patients were still receiving treatment at 12 months.

The median OS was not reached; OS at 6 and 12 months was 100% and OS at 18 months was 83% (95% CI: 27%, 97%).

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Because LIBRETTO-001 is a single-arm trial, other studies needed to be obtained to provide evidence to inform an ITC with selpercatinib in each of the two populations.

3.3.1 RET-mutant medullary thyroid cancer

The company stated that only two trials were identified that were RCTs (including a placebo arm, to be used as a proxy for BSC) and reported results in *RET*-mutant populations: the EXAM trial (cabozantinib versus placebo) and the ZETA trial (vandetanib versus placebo).[5, 9, 10, 17] However, the company stated that ZETA trial did not report PFS and OS KM results for a *RET*-mutant subgroup, only results for ORR. Also, several covariates relevant to the matching adjusted indirect comparison (MAIC) analysis (see Section 3.4) were not reported in the ZETA trial, and treatment crossover from the placebo arm to the vandetanib arm was permitted in the trial. Therefore, the EXAM trial was selected as the most appropriate data source to compare selpercatinib versus BSC, using the placebo arm as a proxy.

The EXAM trial was an international, double-blind, RCT enrolling patients with locally advanced or metastatic MTC. N=109 patients were randomised to placebo.[9, 17] While positive *RET*-mutation status was not required in the EXAM trial, baseline characteristics, only for the cabozantinib arm, and PFS results were available for a *RET*-mutant subgroup of the patient population. However, OS KM data were only reported for a *RET* M918T-positive subgroup. Clinical effectiveness results were also not reported separately for the systemic therapy-naïve and pre-treated patient populations.

EAG comment: Although crossover could produce a bias in the outcome for OS in the placebo arm of ZETA, it would not apply to PFS because it was only permitted on progression.[18] However, it is true that only 50% patients in ZETA were known to be mutation positive and so the EAG does agree that EXAM was possibly the more appropriate of two trials considered.[19] However, because only an unanchored ITC (single arm only) was feasible, it is unclear why the company only conducted searches for all study designs for the *RET*-altered TC and MTC populations. For the wider TC and MTC populations, only RCTs were considered as the source of comparator data. The EAG also had serious concerns about the searches used to retrieve studies for the systematic review (see Section 3.1) and considers that the application of different study design criteria to the *RET*-altered and the wider TC and MTC populations was not appropriate. It was also the conclusion of the Committee in TA742 that, based on the same data source, the results of the MAIC were uncertain because of limitations of the EXAM trial was a comparator data source in this population.[4] This is therefore a key issue.

3.3.2 RET fusion-positive thyroid cancer

The company stated that following a feasibility assessment, the SELECT (lenvatinib versus placebo) and DECISION (sorafenib versus placebo) trials were identified as potential data sources for BSC in this population.[10, 20]

Both SELECT and DECISION were double-blind RCTs enrolling patients with differentiated thyroid cancer. In both trials, treatment crossover from the placebo to the active treatment arm were permitted at disease progression.[10, 20] However, KM OS curves, adjusted for crossover using the rank preserving structure failure time (RPSFT) method, were only available for the SELECT trial.[10] Therefore, the SELECT trial was selected to represent the most appropriate proxy for BSC, which is aligned with the approach accepted in TA535 and TA742.[4] Unfortunately, *RET* status was not available for SELECT. Also, although ORR and PFS data were reported separately for the systemic therapy naïve and experienced subgroups, OS data were only available for the intention-to-treat (ITT) population, including patients who were systemic therapy naïve and systemic therapy experienced.

EAG comment: The EAG agree that SELECT is probably more appropriate than DECISION because of the adjustment for crossover, although such adjustment is not guaranteed to remove all bias due to crossover.[21] This is also an improvement on TA742 where adjusted data were not available.[4]

Nevertheless, the Committee in TA742 based their conclusion that the results of the ITC were uncertain on limitations of SELECT that included more than crossover, in particular differences in proportion of systemic therapy naïve.[4] This is notwithstanding the finding of little difference in treatment effect on PFS in people with treated disease (hazard ratio [HR] 0.22; 95% CI 0.12 to 0.41) versus the overall population (HR 0.21; 95% CI 0.16 to 0.28).[4] The EAG also had serious concerns about the systematic review, as described in Section 3.2 and so this is a key issue.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 RET-mutant medullary thyroid cancer

As stated in Section 3.3, PFS and OS outcomes were not reported separately for the systemic therapy naïve and experienced patients in EXAM. Therefore, the company used the any-line *RET*-mutant MTC patient population from the LIBRETTO-001 trial to better match the EXAM trial.

In the MAIC, the LIBRETTO-001 trial data were adjusted using propensity score weighting (PSW) based on a logistic regression model with independent variables based on the baseline characteristics that the company identified as treatment effect modifiers and/or prognostic, according to technical support document (TSD) 18.[22] These variables were those that were reported in both trials and validated by clinical experts. Matching was to the cabozantinib arm of EXAM because of missing baseline characteristics in the placebo *RET* positive subgroup of the placebo arm (Table 3.44).

The company stated that there was sufficient overlap in these variables between the trials, as indicated by no extreme weights (Figure 3.20).

The results are shown in Table 3.45.

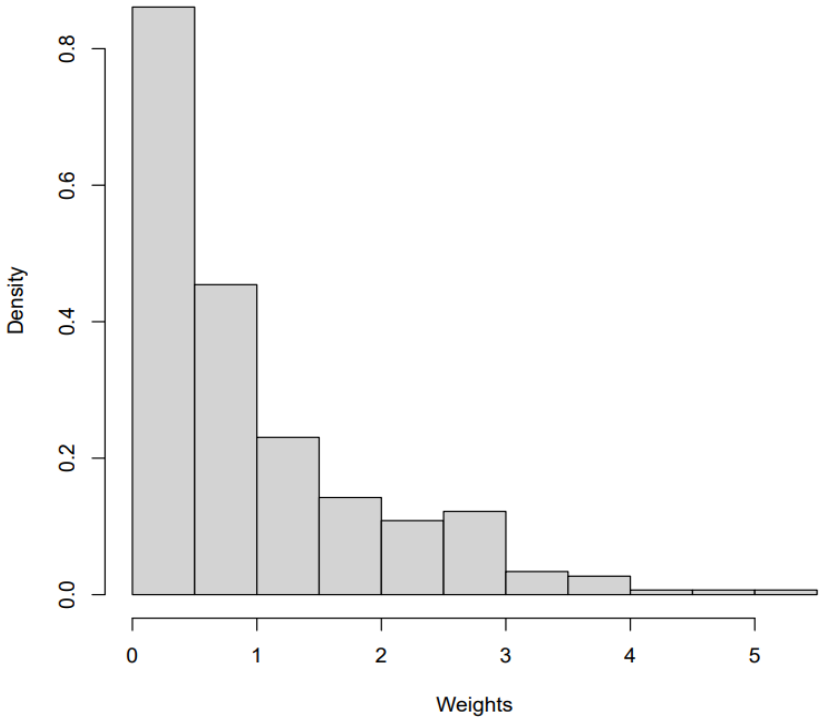
Table 3.44: Matching baseline characteristics between LIBRETTO-001 and EXAM before and after matching

	LIBRETTO-001 any-line (before matching; N=295)	LIBRETTO-001 any-line (after matching; (N_{eff}=157)	EXAM *RET*-mutant cabozantinib (N=107)	EXAM Placebo (N=111)
Age, mean (SD)	56.0 ± 15.1	55.0 (15.2)	55.0 (15.2)	NR a
Weight (kg), mean (SD)	73.1 ± 21.0	74.0 (21.0)	74.0 (21.0)	NR
ECOG PS 0 (%)	37.6	61.7	61.7	50.5
Sex (% male)	61.0	68.2	68.2	63.1
Smoking (% never)	59.7	51.4	51.4	NR
RET M918T mutation positive (%)	62.7	74.6	74.6	52.3
Prior TKI/MKI therapy (%)	54.6	21.5	21.5	21.6

Based on Table 38, CS.[5]
[a] Mean age for patients in the placebo arm of the EXAM trial is not available; Median age is 55.0 years.

	LIBRETTO-001 any-line (before matching; N=295)	LIBRETTO-001 any-line (after matching; (N_{eff}=157)	EXAM *RET*-mutant cabozantinib (N=107)	EXAM Placebo (N=111)
CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MKI = multikinase inhibitor; N_{eff}: effective sample size; NR = not reported; *RET* = rearranged during transfection; SD = standard deviation; TKI = tyrosine kinase inhibitor				

Figure 3.20: Distribution of weights in the MAIC



Based on Figure 27, CS.[5]
CS = company submission; MAIC: matching-adjusted indirect comparison.

Table 3.45: Comparison of PFS and OS for selpercatinib (LIBRETTO-001) versus placebo (EXAM) before and after matching

	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Unweighted	0.07 (0.04, 0.10)	<0.001	0.21 (0.14, 0.32)	<0.001
Weighted	0.05 (0.03, 0.09)	<0.001	0.11 (0.07, 0.18)	<0.001
Based on Table 39, CS.[5] CI = confidence intervals; CS = company submission; HR = hazard ratio; OS = overall survival; PFS = progression-free survival				

EAG comment: The EAG agree that the matching of the characteristics identified has been successful and these were the same characteristics as in the original TA742.[4] It should be noted that since the LIBRETTO-001 trial has recruited more patients since TA742, (N=295 versus 212), there might have been a little decrease in uncertainty in estimating the treatment effect of selpercatinib versus BSC in *RET*-mutant medullary thyroid cancer. However, the same problem of mixed line of therapy as referred to by the appraisal committee in TA742 applies still applies.[4] Also, the problem with any MAIC where the adjustment is from the intervention to the comparator trial that the treatment effect estimate is more applicable to the comparator trial also still applies.[22]

3.4.2 RET fusion-positive thyroid cancer

The company stated that a MAIC could not be performed due to insufficient comparability between the trials. The company also argued that the ITC needed to use the any-line population from both trials because data on prior systemic therapy were not available for OS.[5] The results are shown in Table 3.46.

Table 3.46: Comparison of PFS and OS for selpercatinib (LIBRETTO-001, any-line) versus placebo (SELECT, ITT population)

Treatment comparison	HR (95% CI)	p-value
PFS: selpercatinib versus BSC (placebo)	[redacted]	[redacted]
OS: selpercatinib versus BSC (placebo)	[redacted]	[redacted]
Based on Table 43, CS. BSC = best supportive care; CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival		

EAG comment: Given that lack of comparability is the main impetus for population adjustment, notwithstanding the challenges of lack of overlap or small effective sample size (ESS), the EAG requested in the clarification letter that the company conduct a MAIC.[23] They were asked to describe the method including tests of overlap, as specified in NICE Decision Support Unit (DSU) TSD 18.[22] In response, the company conducted a MAIC and demonstrated the lack of overlap as evidenced by extreme weights and very large drop in ESS.[1] The EAG therefore agree with the company that the MAIC should be treated with extreme caution. It therefore remains unclear what the effect of better comparability might be, but the naïve comparison seems to be the best type of analysis with the available data.

The EAG also requested that the company conduct an ITC for PFS using the prior systemic therapy population of both trials in order that the effect of prior systemic therapy can be observed. The company responded by performing this, albeit without using population adjustment, citing the lack of overlap as demonstrated for the whole population mentioned above. This showed results that were largely consisted with those for the whole population i.e., PFS HR [95% CI] of [redacted] instead of [redacted] Of course, one cannot be sure of what the results would be for OS or if there was greater comparability between the trials, but it does appear that prior experience has little substantive effect on the treatment effect.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

Technology appraisal guidance TA742 (Selpercatinib for treating advanced thyroid cancer with *RET* alterations) states:

"Selpercatinib is recommended for use within the Cancer Drugs Fund, as an option for treating:

- *advanced RET fusion-positive thyroid cancer in adults who need systemic therapy after sorafenib or lenvatinib*
- *advanced RET-mutant medullary thyroid cancer in people 12 years and older who need systemic therapy after cabozantinib or vandetanib.*

It is recommended only if the conditions in the managed access agreement are followed."

The following text describes why the appraisal committee made these recommendations:

"People with advanced RET fusion-positive thyroid cancer are usually first offered a partial or full thyroidectomy. This is followed by radioactive iodine and then lenvatinib or sorafenib. People with advanced RET-mutant medullary thyroid cancer are usually offered a partial or full thyroidectomy, followed by cabozantinib.

Clinical trial evidence for selpercatinib is highly uncertain because it is based on an ongoing single-arm trial and not all subpopulations represent NHS practice. The results comparing selpercatinib indirectly with best supportive care are also highly uncertain.

Selpercatinib could be cost effective if more data becomes available from the ongoing trial that shows people live longer with treatment. Data from the trial and NHS practice would also help address the uncertainty about its clinical effectiveness. Selpercatinib is therefore recommended for use in the Cancer Drugs Fund so that more data can be collected."[4]

The areas of clinical uncertainty, listed in the managed access agreement, are:

- *"Immaturity of the progression-free and overall survival data in both the RET mutant medullary thyroid and RET fusion positive thyroid cancer populations.*
- *Generalisability of data from the LIBRETTO-001 study to UK clinical practice in terms of prior treatment."*[15]

The efficacy and safety evidence for selpercatinib presented in Section B.2 of the CS informed by the most recent data cut for *RET*-altered TC and MTC in the LIBRETTO-001 trial: the 13 January 2023 DCO. This DCO provides more mature survival data (PFS and OS).

With respect to the generalisability of data from the LIBRETTO-001 study to UK clinical practice, in terms of prior treatment, this issue remains when considering the any-line *RET*-mutant MTC and any-line *RET* fusion-positive TC populations; these are the populations used in ITCs to generate estimate of the comparative clinical effectiveness of selpercatinib versus BSC and to inform cost-effectiveness modelling.

In their response to clarification questions, the company have provided subgroup analyses for populations relevant to UK clinical practice, in terms of prior treatment, i.e., people with advanced *RET* fusion-positive thyroid cancer TC who have received prior treatment with sorafenib [redacted] lenvatinib, and people with advanced *RET* mutation-positive MTC who have received prior treatment with cabozantinib [redacted] vandetanib.[1] The results of these analyses are included in Section 3.2.5.

The ITCs, presented in the CS, used the any-line *RET*-mutant MTC and any-line *RET* fusion-positive TC populations from the LIBRETTO-001 study because the trials (EXAM and SELECT) which provided comparator data (placebo as a surrogate for BSC) did not report OS and PFS results separately for systemic therapy-naïve and systemic therapy experienced patients. The one exception was for PFS in the *RET* fusion-positive thyroid cancer population, which prompted the EAG to request this analysis. The results showed little difference in HR between any-line and systematic therapy experienced populations, although it is unclear if this would be the case for OS or for *RET*-mutant MTC. The EXAM and SELECT trials were identified in an SLR conducted by the company, however, the EAG does not consider that the design of this SLR was appropriate to adequately explore all potential sources of comparator data. Whilst a good range of bibliographic databases, conferences and trials registers were searched, the EAG found the searches to be both overcomplicated and restrictive, particularly in relation

to the condition facet, which may have affected the overall recall of results. This means that this is a key issue.

The EAG considers that the high level of uncertainty, regarding results comparing selpercatinib indirectly with BSC, noted in TA742, remains a key issue.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and resource use identification presented in the CS. The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[12] The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS reported that no searches were undertaken to identify relevant studies on cost effectiveness. Searches conducted to find HRQoL and cost/health care resource use data were reported in Appendix H and were undertaken in August 2019. A summary of the sources searched is provided in Table 4.1. Table 4.1: Data sources searched for HRQoL and cost/resource use studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Not reported	2017-2019/08/12	12.8.19
MEDLINE	PubMed	2017-2019/08/12	12.8.19
EconLit	Not reported	2017-2019/08/12	12.8.19
Cochrane Library (individual elements not reported)	Not reported	2017-2019/08/12	12.8.19
Additional resources			
NHS EED	CRD website	From inception	7.10.19
HTA Database	CRD website	From inception	7.10.19
CEA Registry	Internet	From inception	8.10.19
ICER	Internet	From inception	8.10.19
Conferences			
ISPOR ASCO ESMO IASLC	All indexed in Embase therefore websites not searched		
HTA websites			
CADTH NICE SMC	Internet		8.10.19

ASCO = American Society of Clinical Oncology; CADTH = Canadian Agency for Drugs and Technology in Health; CEA Registry = Cost-Effectiveness Analysis Registry; CRD = Centre for Reviews and Dissemination; CS = company submission; ESMO = European Society for Medical Oncology; HTA = Health Technology Assessment; IASLC = International Association for the Study of Lung Cancer; ICER = Institute

Resource	Host/Source	Date Ranges	Date searched
for Clinical and Economic Review; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS EED = National Health Service Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium			

EAG comment:

- In Appendix G the company stated that *"As thyroid cancer is a rare type of cancer, and there are no other selective RET kinase inhibitors currently available to patients, it was not considered necessary to conduct a SLR to identify relevant previous economic evaluations*". In order to demonstrate the validity of that claim, the EAG requested that the company conduct a full SLR to confirm that there were no relevant economic papers on this topic. The company declined stating that their targeted literature review (TLR) of previous NICE technology appraisals (TAs) would have the identified the most pertinent economic evaluations relating to the treatment of these patients in UK clinical practice. Details of the TLR searches were not reported in the CS and the EAG remains concerned that there is no real evidence to support these claims.
- A single set of searches was undertaken in August 2019 to identify to identify relevant studies on HRQoL, resource use and cost data. The CS reported that "*for efficiency, recent relevant NICE appraisals were used to identify data that have been accepted by NICE as the best available at the time of those appraisals, and a systematic search for more recently published data was conducted and were limited to studies published from 1st January 2017 to August 2019*."[5, 11] The CS, Appendix H and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.
- In addition to bibliographic database searches, a good range of Health Technology Assessment (HTA) organisation websites, grey literature resources and conferences proceedings were searched. Bibliographic lists of relevant articles and systematic reviews were searched for relevant primary articles that were not identified by the electronic searches. The searches were well structured and transparent.
- As the searches reported in Appendix H were conducted in 2019, the EAG asked the company to provide an update to ensure that no new relevant studies had been published in the five years since these searches were conducted. The company declined to update the searches stating that "*A health-related quality of life (HRQoL) and healthcare cost and resource use (HCRU) use study SLR update was unable to be conducted by Lilly within the timeframe of the clarification questions. However Lilly maintain that the most relevant HCRU and utility data was used to support the development of this submission*."[1] As with the economics searches, the EAG remains concerned that there is no real evidence to support these claims. To explore this further the EAG ran a simplified update of the HRQoL element of the CS searches and identified 741 additional references in Embase which may have included relevant papers, including Huang 2024 and Houten 2021 (See Section 4.1.4 for further detail).[24, 25]
- The EAG noticed an error in the search term for utilities in facet 2 of the Embase strategy. In four instances the word "utility" appears to have been replaced by "107tility*". The company confirmed that this was due to a reporting error, however the EAG also noted that the truncation symbol had been incorrectly applied after the 'y' rather than after the 't', which would fail to capture the synonym 'utilities'. However it was correctly applied in the PubMed search, which may have mitigated against some loss of recall.
- None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.

- The EAG that noted that a study design filter was employed in the search of EconLit. Given that this is specialised economics resource and a search for the condition alone only retrieved one record, this appears to be inappropriate, but given that only a single result was omitted it is unlikely to have affected the overall recall of results.
- For details of further limitations please refer to the 2020 EAG report for additional comments.[13]

4.1.2 Inclusion/exclusion criteria

4.1.3 The in- and exclusion criteria used by the company for HRQoL and cost and resource use studies are presented in Appendix H, Table 39 (search date August 2019).[11] The EAG considers the in- and exclusion criteria to a large extent suitable to capture all relevant evidence, though some relevant papers may have been missed due to exclusion of papers based on language. Findings of the cost-effectiveness review

The PRISMA flow diagram for the quality of life and cost and resource use studies is presented in Figure 3 of appendix H and includes studies for both NSCLC and thyroid cancer.[11] The PRISMA diagram indicates that 292 records were included from the SLR. However, as seen in Tables 40 and 42 respectively, a total of four quality-of-life studies and 30 cost-resource use studies (all from the August 2019 search) were included. Table 41 shows that a total of 34 studies were excluded during screening. The company did not consider any of the four included HRQoL studies suitable to patients with *RET*-mutant MTC or *RET* fusion-positive TC.

A TLR was conducted for cost-effectiveness studies, as the company decided not do an SLR to identify relevant studies on cost effectiveness. This resulted in a selection of five previous NICE TAs in thyroid cancer indications that could inform the model structure, functionality, assumptions, and data sources. A summary list is provided in Table 52 of the CS. **EAG comment**: As in the EAG's critique for TA742,[13] it was very difficult to follow the review given that it was conducted for both NSCLC and TC and no disaggregation was given in the PRISMA diagram. It is unclear to what extent information was missed due to the company decision not to conduct a full SLR for economic evaluations.

The sum of the in- and excluded studies is 68 studies, far less than the 292 studies that were included according to the PRISMA diagram. This raises the question whether the remaining HRQoL and cost and resource use studies shown as included in the PRISMA diagrams all pertain to NSCLC, or that another reason exists for this discrepancy.

It is concerning that the HRQoL study by Fordham et al, used by the company in the model that was originally submitted, was not identified in the HRQoL SLR.[26] It is unclear how many other studies may have been missed.

4.1.4 Conclusions of the cost-effectiveness review

The CS and response to the clarification letter provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data of selpercatinib for the treatment of advanced thyroid cancer with *RET* alterations. Searches were transparent and reproducible, and appropriate strategies were used. A broad range of databases and grey literature were searched.

Overall, the EAG has various concerns about the literature review. First, no effort was made to include more recent HRQoL studies through a new SLR, as the literature search was not updated from TA742. When asked to provide such update during clarification, the company declined this request. From a quick search the EAG was able to identify 741 studies published since August 2019. An incomplete (due

to time constraints) screening of title and abstract already identified two potentially relevant papers, i.e., a mapping study by Huang et al. 2024 that was done in patients with papillary thyroid carcinoma,[24] and a systematic review by Houten in 2021.[25] It is not clear how many other studies might have been identified if a proper update of the SLR had been performed.

In addition, the SLR was not used to search for economic evaluations, instead a TLR was done for this purpose. However, no details were provided about the approach used for the TLR on cost-effectiveness studies, therefore the EAG cannot comment on the appropriateness of this search.

Features of the models used in NICE TA742, TA516 and TA535,[4, 27, 28] as identified through the TLR, were utilised to build the current model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	According to NICE reference case
Perspective on costs	NHS and PSS	According to NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	According to NICE reference case
Synthesis of evidence on health effects	Based on systematic review	No head-to-head evidence between selpercatinib and BSC was available. An unanchored MAIC was used to compare selpercatinib with BSC in the *RET*-mutant MTC population and a naïve ITC was performed for the *RET* fusion-positive TC population.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects are expressed in QALYs. In the CS, the utility values used in the model were estimated using a vignette study, in which members of the general population valued health state descriptions designed to represent DTC cancer health states.[26] In the model submitted in response to the clarification letter, utilities were used that resulted from mapping EORTC QLQ-C30
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	

Element of health technology assessment	Reference case	EAG comment on CS
		data from the TC population in LIBRETTO-001.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	According to NICE reference case for updated company model
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	According to NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	According to NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	According to NICE reference case

BSC = best supportive care; CS = company submission; EAG = Evidence Assessment Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; MTC = medullary thyroid cancer; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer; UK = United Kingdom

4.2.2 Model structure

The model constructed by the company has the same structure as the model used in TA742,[4] i.e., a cohort-based partitioned survival model with three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. The model structure does not allow for patients to improve their health state, i.e., move from PD to PF. The proportion of patients in the PF state is defined by the PFS curve, the proportion of patients in the death state is defined by the OS curve and the proportion of patients in the PD state is defined by the proportion of patients alive minus the proportion progression-free. The model applies a cycle length of one week.

EAG comment: The model structure is considered appropriate for the decision problem.

4.2.3 Populations

The population for this TA consists of two distinct populations, i.e., patients with *RET*-mutant MTC and patients with *RET* fusion-positive TC, each of which will be discussed below.

4.2.3.1 RET-mutant MTC

The *RET*-mutant MTC patient population that is considered in the cost effectiveness analysis consists of adults and adolescents aged 12 years and older with advanced *RET*-mutant MTC who require systemic therapy after prior treatment with cabozantinib or vandetanib. For the model, data was used from the MTC patient population in the LIBRETTO-001 trial.[29, 30] Data from both the 'MTC: Cab/Van' analysis set (n=152; patients with MTC who had received one 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) were pooled, in order to align with the available data from the EXAM trial for BSC.[9]

The patients with *RET*-mutant MTC from the any-line population in LIBRETTO-001 had a mean age of [redacted] and consisted of 39.0% females;[14, 30] these values have been used as baseline characteristics for the modelled cohort.

4.2.3.2 RET fusion-positive TC

The *RET* fusion-positive TC patient population that is considered in the cost effectiveness analysis consists of adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy after prior treatment with sorafenib or lenvatinib. For the model, data was used from the TC patient population in the LIBRETTO-001 trial.[29, 30] Data from both the systemic therapy naïve patients (n=24) and the patients that had previously received systemic therapy (n=41) were pooled, in order to align with the available data from the SELECT trial for BSC.[10]

The patients with *RET* fusion-positive TC from the any-line population in LIBRETTO-001 had a mean age of [redacted] and consisted of 50.8% females;[14, 30] these values have been used as baseline characteristics for the modelled cohort.

EAG comment: There is a mismatch between the population addressed in this TA and the population from which trial data was used to assess PFS and OS. The population of relevance for this TA are patients who require systemic treatment after a prior treatment, whereas trial data is used from the 'any-line' patient, i.e., both those naïve to systemic treatment and those who received such treatment before. Given that patients with prior treatment show lower OS and PFS compared to the 'any-line' patients (see Figures 3.7 to 3.14), it appears unlikely that the current approach to assessing the cost-effectiveness of selpercatinib versus BSC will lead to an accurate estimate of the incremental cost-effectiveness ratio (ICER).

4.2.4 Interventions and comparators

Selpercatinib, the intervention under consideration, is self-administered orally twice daily (BID) until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation. The selpercatinib dose included by the company in the economic model is 160 mg orally BID, which is the dose for adult and adolescent patients weighing ≥ 50 kg. This assumption was based on the 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.

When patients require dose reductions whilst receiving selpercatinib, the selpercatinib summary of product characteristics (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.[6]

For both the RET-mutant MTC and the RET fusion-positive TC populations, the comparator included in the model was BSC, in line with current clinical practice in the UK. Best supportive care is assumed to consist of the routine care and monitoring. For the RET-mutant MTC population, the company considered the placebo arm of the EXAM trial a suitable proxy for BSC, as determined in TA516 and TA742 and also discussed in Section B.2.9.1.[4, 27] For the RET fusion-positive TC population, the company considered the placebo arm in the SELECT trial to represent a suitable proxy for BSC; this is aligned with TA535 and TA742.[4, 28] Whilst the SELECT trial only included patients with DTC, the

placebo arm of the trial was 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) since patients with other subtypes of TC have no suitable treatment options other than BSC.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective, in line with the NICE reference case.[31] Discount rates of 3.5% per annum are applied to both costs and benefits. The time horizon used in the model is 35 years, which represents a lifetime time horizon as per the NICE reference case.[31]

EAG comment: In the CS, the company states that a 35-year time horizon was used, however, deterministic results presented in Appendix J.3 are consistent with a 25-year time horizon. The revised company results after clarification[1] show that for the *RET* fusion-positive TC population the time horizon had been set to 35 years, but for the *RET*-mutant MTC population a 25-year time horizon had been used. Thus, in Section 5, the EAG has corrected this and presents the company base-case for a time horizon of 35 years. Note that the impact of increasing the time horizon from 25 to 35 years is minimal.

4.2.6 Treatment effectiveness and extrapolation

Survival analyses for the selpercatinib arm were performed using data from the LIBRETTO-001 trial. In the absence of head-to-head trial data comparing the clinical effectiveness of selpercatinib against BSC, the company relied on ITC analyses to estimate PFS and OS in the BSC arms of the model. Details on these indirect analyses methods are provided and discussed in Section 3.4, while the details specific to the model implementation on the indirect treatment comparison results are explained below.

The company conducted the survival analyses using the recommendations by the NICE DSU TSD 14 on survival data extrapolation.[32] Seven parametric distributions (exponential, Weibull, Gompertz, lognormal, log-logistic, gamma, and generalised gamma) were fitted to extrapolate OS, PFS, and time on treatment (the latter included in the electronic model only) data from the LIBRETTO-001 trial. The company further explored the use of flexible models, i.e., spline models with 1, 2 or 3 knots[32] based on the algorithm by Royston and Parmar et al (2002).[33] To fit OS data from the *RET*-fusion positive TC population, the company further explored the option of the piecewise exponential model. For the BSC arms of both the *RET*-mutant MTC and the *RET*-fusion positive TC populations, the analyses were based on reconstructed pseudo-IPD from the EXAM[9, 17, 34] and the SELECT[10] trials, respectively. Stratified and unstratified models were explored throughout the survival analyses. With stratified models the company explained they referred to models where all parameters varied by treatment, did not assume proportional hazards (PH) or constant acceleration factors, while the model fit statistics of the alternative parametric functions can be compared across all models in contrast to models fitted independently to each treatment arm for which model fit statistics cannot be compared across all models.

4.2.6.1 Overall survival of RET-mutant MTC

For the selpercatinib arm, 19 alternative stratified and unstratified parametric survival models were fitted to weighted OS data from the LIBRETTO-001 trial as these were generated through the unanchored MAIC analyses. The unanchored MAIC analyses for the *RET*-mutant MTC population compared data from the any-line MTC patient population (n=295) of the LIBRETTO-001 trial, comprising of patients with MTC who had received one or more lines of prior cabozantinib or

vandetanib (n=152) and patients with MTC who were naïve to cabozantinib and/or vandetanib (n=143), with data from the EXAM trial.[9, 29, 30, 34] Patients from the LIBRETTO-001 trial were matched (ESS=157) to the *RET*-mutant population receiving cabozantinib in the EXAM trial (n=107), as patient characteristics from the placebo arm of the *RET*-mutant subgroup treated in the EXAM trial were not available. To inform OS of the BSC arm, the *RET* M918T-positive subgroup treated with placebo (n=45) of the EXAM trial was used, as OS KM data for the *RET*-mutant subgroup treated with placebo was not available.[9] Referring to TA742, the company justified this approach by noting that UK clinical experts in TA742 confirmed that placebo outcomes in the *RET* M918T-positive group may be similar to the *RET*-mutant group as a whole.[4]

The PH assumption was assessed using the log-cumulative hazard plot (Figure 5 in Appendix N), the Schoenfeld residual plots (Figure 9 in Appendix N), and the global Schoenfeld residuals test of PHs resulting in a p-value of [redacted] (for the weighted data of the selpercatinib arm).[11] Referring to these figures and the Schoenfeld test, the company concluded that there was no evidence to suggest a violation of the PH assumption for the OS of selpercatinib versus BSC of the *RET*-mutant MTC population.

Table 4.3 below summarises the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for each of the 19 parametric distributions (including non-stratified and stratified models) that were fitted to the weighted OS curve for selpercatinib and the unweighted OS curve for the *RET* M918T-positive subgroup receiving placebo. Based on the statistical goodness of fit criteria, the loglogistic and exponential models presented the best fit to the observed KM data.

Table 4.3: AIC and BIC statistics for OS parametric models for selpercatinib and BSC, *RET*-mutant MTC

Model	AIC	Rank (AIC)	BIC	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]

Model	AIC	Rank (AIC)	BIC	Rank (BIC)
Based on Table 60 of the CS.[5] AIC = Akaike information criterion; BIC = Bayesian information criterion; BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; OS = overall survival; *RET* = rearranged during transfection				

Figure 4.1 and Figure 4.2 below present the long-term OS extrapolations as estimated based on the alternative parametric models, while Table 4.4 and Table 4.5 present the corresponding median and landmark OS estimates at 5, 10 and 20 years.

Figure 4.1: OS Extrapolations for selpercatinib, RET-mutant MTC

Based on Figure 35 of the CS.[5]
CS = company submission; MTC = medullary thyroid cancer; OS = overall survival; Prop = proportion; *RET* = rearranged during transfection

Figure 4.2: OS Extrapolations for BSC, *RET*-mutant MTC [redacted]Based on Figure 36 of the CS.[5]
BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; OS = overall survival; Prop = proportion; *RET* = rearranged during transfection.

To justify the choice of their preferred parametric function for OS extrapolations, the company used the feedback that was provided by clinical experts during the ongoing appraisal for selpercatinib in patients with untreated, advanced thyroid cancer with *RET* alterations (ID6132) (see Table 4.4).[35] Based on this feedback it was concluded that the stratified Weibull extrapolation option would be the most appropriate to model OS for selpercatinib and BSC as it presented the most pessimistic long-term OS predictions for selpercatinib. The company further commented that the selection of the stratified Weibull parametric model aligned with the Committee preferences in TA742.[4] However, although the stratified Weibull led to the most pessimistic 10-year OS predictions ([redacted] alive) as compared to the other models, it still overestimates OS survival versus the estimates provided by the clinical experts ranging from [redacted] to [redacted] as shown in Table 4.4. To resolve this issue the company implemented an adjustment factor of 2.0 to the OS hazard rate of selpercatinib from five years and onwards. The OS estimates following the adjustment are also presented in Table 4.4. To model the OS of the BSC arm, the stratified Weibull function was also used, referring to the NICE DSU recommendation of survival analyses which require the same parametric model to be used when fitting independent survival models to different treatment arms (unless otherwise justifiable). Nonetheless, no adjustment factor was implemented for the OS of BSC, as the 10-year and 20-year OS with the stratified Weibull matches the estimates from the clinical experts (see Table 4.5). Finally, the company assumed that no further benefits would be accrued after 35 years. The stratified gamma extrapolation was explored in a scenario analysis, also combined with the 2.0 adjustment factor (only for the selpercatinib arm).

Table 4.4: Median and landmark OS survival estimates for selpercatinib, *RET*-mutant MTC

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	[redacted]	[redacted]	[redacted]	[redacted]

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Median and landmark survival as estimated by the alternative parametric functions				
Stratified spline knot 3[b]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline knot 2[a]	[redacted]	[redacted]	[redacted]	[redacted]
Spline knot 2[b]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma[b]	[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]
Median and landmark survival with adjustment factor applied				
Stratified Weibull (2.0 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 61 of the CS.[5]

[a]The EAG noticed that the stratified spline 2 model predictions were not included in Table 61 of the CS and extracted the respective values from the electronic model.

[b]The EAG noticed that in the electronic model median OS for the spline knot 2 was 354.18 whereas for the stratified generalised gamma, the stratified spline knot 2 and the stratified spline knot 3 median OS was more than 400> months. Thus, these values have been corrected in this Table compared to the original.

Note that parametric curves are ordered from highest to lowest 10-year survival.

CS = company submission; MTC = medullary thyroid cancer; NA = not applicable; OS = overall survival; *RET* = rearranged during transfection.

Table 4.5: Median and landmark OS survival estimates for BSC, *RET*-mutant MTC

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	[redacted]	[redacted]	[redacted]	[redacted]
Median and landmark survival as estimated by the alternative parametric functions				
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Stratified spline knot 2[a]	[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]

Based on Table 62 of the CS. [5]
Note that parametric curves are ordered from highest to lowest 10-year survival.
[a]The EAG noticed that the stratified spline 2 model predictions were not included in Table 62 of the CS and extracted the respective values from the electronic model.
BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; NA = not applicable; OS = overall survival; *RET* = rearranged during transfection.

EAG comments: The EAG comments on the analysis of OS for the *RET*-mutant MTC population are presented in the end of Section 4.2.6.2 combined with the EAG comments on the analysis of PFS for the *RET*-mutant MTC population.

4.2.6.2 Progression-free survival of RET-mutant MTC

Similar to the OS analysis, alternative stratified and unstratified parametric survival models were fitted to the weighted PFS data from the LIBRETTO-001 trial as these were generated through the unanchored MAIC analyses from the any-line MTC patient population of the LIBRETTO-001 trial (n=295) and the *RET*-mutant population receiving cabozantinib in the EXAM trial.[9, 29, 30, 34] To inform the PFS of the BSC arm, the company used the *RET*-mutant population receiving placebo (n=62) in the EXAM trial.[34]

The PH assumption for the PFS was assessed using the log-cumulative hazard plot (Figure 4 in Appendix N), the Schoenfeld residual plots (Figure 7 in Appendix N), and the global Schoenfeld residuals test of proportional hazards resulting to a p-value of [redacted] for PFS (for the weighted data of the selpercatinib arm).[11] Based on these figures and the Schoenfeld test, the company concluded that there was no evidence to suggest a violation of the PH assumption for the PFS of selpercatinib versus BSC.

Table 4.6 below summarises the AIC and BIC values for each survival model that was fitted to the weighted PFS curves for selpercatinib and the unweighted PFS curve for the *RET*-mutant subgroup

receiving placebo in the EXAM trial. Based on the statistical goodness of fit criteria, the generalised gamma, the stratified generalised gamma, the stratified Weibull and stratified 3-knot spline showed the best statistical fit, followed by the stratified Gompertz and the stratified 2-knot spline.

Table 4.6: AIC and BIC statistics for PFS parametric models for selpercatinib and BSC, *RET*-mutant MTC

Model	AIC	Rank (AIC)	BIC	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]

Based on Table 57 of the CS.[5]

[a] Table 57 of the CS noted that the generalised gamma extrapolation did not converge, and therefore included NAs in the AIC/BIC rankings. The EAG does not agree with the company's approach in not presenting the AIC/BIC ranking and reordered the models including the generalised gamma and stratified generalised gamma.

[b] Table 57 of the CS noted that the stratified generalised gamma extrapolation did not converge for cabozantinib only, and therefore included NAs in the AIC/BIC rankings. The EAG does not agree with the company's approach in not presenting the AIC/BIC ranking and reordered the models including the generalised gamma and stratified generalised gamma.

AIC = Akaike information criterion; BIC = Bayesian information criterion; BSC = best supportive care; CS = company submission; EAG = Evidence Assessment Group; MTC = medullary thyroid cancer; NA = not applicable; PFS = progression-free survival; *RET* = rearranged during transfection

Figure 4.3 and Figure 4.4 below present the long-term PFS extrapolations as estimated based on the alternative parametric models, while Table 4.7 and Table 4.8 present the corresponding median and landmark PFS estimates at 5, 10 and 20 years.

Figure 4.3: PFS Extrapolations for selpercatinib, *RET*-mutant MTC

Based on Figure 33 of the CS.[5]
CS = company submission; MTC = medullary thyroid cancer; PFS = progression-free survival; Prop = proportion; *RET* = rearranged during transfection

Figure 4.4: PFS Extrapolations for BSC, *RET*-mutant MTC

Based on Figure 34 of CS.[5]

BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; PFS = progression-free survival; Prop = proportion; *RET* = rearranged during transfection

The company's preferred parametric function for PFS extrapolations was primarily justified by referring to the feedback that was provided by clinical experts during the ongoing appraisal for selpercatinib in patients with untreated, advanced thyroid cancer with *RET* alterations (ID6132) summarised in Table 4.7 below.[35] Based on this feedback it was concluded that the loglogistic extrapolation would be the most appropriate to model PFS for selpercatinib and BSC, also aligning with the Committee preferences in the original appraisal of selpercatinib in TA742.[4] The gamma and spline knot 1 extrapolations were explored in scenario analyses.

Table 4.7: Median and landmark PFS survival estimates for selpercatinib, *RET*-mutant MTC

Models/Clinical Experts	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	[redacted]	[redacted]	[redacted]	[redacted]
Median and landmark survival as estimated by the alternative parametric functions				
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]

Based on Table 58 of the CS.[5]

Note that parametric curves are ordered from highest to lowest 10-year survival.

[a] The generalised gamma extrapolation did not converge.

CS = company submission; MTC = medullary thyroid cancer; NA = not applicable; PFS = progression-free survival; *RET* = rearranged during transfection

Table 4.8: Median and landmark PFS survival estimates for BSC, *RET*-mutant MTC

Models/Clinical Experts	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	[redacted]	[redacted]	[redacted]	[redacted]
Median and landmark survival as estimated by the alternative parametric functions				
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]

Based on Table 59 of the CS.[5]

[a] The generalised gamma extrapolation did not converge.

Note that parametric curves are ordered from highest to lowest 10-year survival.

BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; NA = not applicable; PFS = progression-free survival; *RET* = rearranged during transfection

EAG comment: Although, when compared to the original company submission TA742,[4] the current appraisal presents longer follow-up data from the LIBRETT0-001 trial (using the 13 January 2023 DCO), the EAG's original concerns around the appropriateness of the data sources used to inform the survival analyses still pertain to the current appraisal:

a) Firstly, to inform the OS and PFS data, the company used survival data from the any-line MTC patient population from the LIBRETTO-001 trial for selpercatinib arguing that the "*any-line RET-mutant pooled population from the LIBRETT0-001 trial was used rather than the prior cabozantinib/vandetanib RET-mutant population (MTC: Cab/Van) because the former more closely matches the characteristics of the EXAM trial population, and provides a larger patient-level data set*".[5] Although the EAG agrees with the company that this approach includes survival data for a mixed population (consisting of naïve and previously treated patients) for both selpercatinib and BSC arms, it still remains inconsistent with the population that is relevant for the decision problem of this appraisal, which consists of only previously treated patients.

Despite the company's matching efforts in the MAIC analyses, the key source of uncertainty remains on whether similar conclusions would have been reached if only previously treated patients had been analysed. The EAG's concerns are strengthened by the fact that OS and PFS are substantially lower for previously treated patients than for naïve patients as shown in Table 1.6. of the CSR.[14] To resolve part of this uncertainty, the EAG asked the company to reproduce the survival analyses by removing the patients with MTC who were naïve to cabozantinib and/or vandetanib from the survival analyses and include these results in a scenario analysis. In response (Question B3(f) of the clarification letter), the company declined to conduct this analysis arguing that such an analysis "*is expected to substantially bias results against selpercatinib; the LIBRETTO-001 trial population informing the MAIC would include a higher proportion of patients who had already progressed on prior systemic therapy versus the EXAM trial*."[1] In question B3d, the company substantiated this by adding the proportion of patients with MTC or TC that had not received prior MKI/TKI therapy in the LIBRETTO-001 trial (MTC: [redacted]; TC [redacted] against the respective proportions in the placebo arms of the EXAM (77.5%) and SELECT (79.4%) trials. The EAG concurs with the company's perspective that using prior cabozantinib/vandetanib *RET* mutant-MTC population of the LIBRETTO-001 trial and the any-line *RET*-mutant placebo arm of the EXAM trial would be associated with a bias against selpercatinib. However, considering the existing uncertainties around the comparability of the populations between the two trials, the EAG maintains that it would still be an informative scenario that could represent a lower bound of survival gains for selpercatinib against BSC. In that regards, it is noteworthy that in TA742 the company had used the previously treated patient population (n=19) from the LIBRETTO-001 trial to inform survival of patients with *RET* fusion-positive TC receiving selpercatinib throughout the assessment (clarification question B1),[1] while in the current appraisal the company switched to any-line TC patients to inform the OS and PFS data for this population as explained in Section 4.2.6.3 below. This change had not been requested by the EAG or the Committee in TA742.[35]

b) Secondly, as also summarised in the EAG comments in Section 3.4, although uncertainty in terms of the MAIC analysis for the *RET*-mutant MTC population may have slightly improved with the updated LIBRETTO-001 trial data which considered more patients (N=295 vs. 212) than in TA742, substantial uncertainty remains with regards to the use of an unanchored MAIC. Uncertainty also persists in terms of patients being matched to the cabozantinib arm of the EXAM trial instead of the placebo arm.

c) Thirdly, as also highlighted by the EAG in the selpercatinib appraisal for untreated patients (ID6132),[35] using the placebo arm from the EXAM trial to estimate OS and PFS for the BSC arm may be a good approximation for PFS but not for OS. That is because in the placebo arm of the EXAM trial, 57.7% of the placebo arm patients received a subsequent anti-cancer therapy, with 49.5% of the placebo arm patients receiving a subsequent systemic therapy.[9] This indicates that patients in the placebo arm of the EXAM trial may not appropriately represent BSC patients in NHS clinical practice as these patients is unlikely to receive subsequent treatment upon their disease progression.[35]

d) Fourthly, all parametric models presented by the company overestimated OS predictions as provided by clinical expert opinion, while for PFS only four out of the 19 different parametric models (Gompertz, Weibull, gamma, and loglogistic) provided long-term PFS extrapolations that matched with clinical expectations with the rest of the models also overestimating PFS. To align with the clinical expert feedback on the 10-year and 20-year OS survival estimates of the

selpercatinib arm the company chose the most pessimistic curve in terms of survival extrapolations (stratified Weibull) and implemented an adjustment factor of 2.0 to the OS hazard rate of selpercatinib after five years. The EAG thinks this approach is arbitrary although accepts that it produces more clinically plausible results. The need to adjust the hazard function to ensure clinical plausibility further supports the EAG's concerns around the appropriateness of using the any-line MTC patient population to inform OS predictions for the population of relevance of this appraisal, i.e., pre-treated patients. That is also because the survival of previously treated patients is expected to be overestimated by the improved survival of the naïve patients resulting in survival extrapolations that do not meet with the clinical expert feedback. Moreover, to validate the OS and PFS survival extrapolations the company used feedback from UK clinical experts that was provided during the ongoing ID6132 appraisal of selpercatinib, concerning untreated patients with advanced thyroid cancer with *RET* alterations. During the interviews, UK clinical experts provided estimates of the proportion of patients anticipated to be progression-free following treatment with each treatment at landmark timepoints.[36] It is unclear if clinical experts provided their expectations thinking of treatment-naïve patients (i.e., the target population of ID6132) or a mixed population including previously treated and naïve patients. Considering the observed survival differences between previously treated and treatment-naïve patients, survival predictions for a mixed population would be expected to lie in between the survival of these two groups and it remains unclarified for which population clinical experts provided their long-term expectations in terms of survival.

Although the company presents a variety of models including joint models (assuming PH) and stratified models, it is currently unclear to the EAG if estimation of independent models as per the NICE DSU TSD 14 guidance on survival data extrapolations would provide a better fit.[32] Considering the uncertainties around the survival data and the potential flexibility of the stratified models, the EAG is unsettled if other survival modelling methods would result in models that would better match to the observed data and clinical expectations. To address the uncertainties around the implementation of the current modelling approach for the OS of selpercatinib, the EAG has aligned with the EAG's approach during the appraisal for selpercatinib in untreated patients (ID6132)[35] and has run additional scenarios in which the adjustment factor was varied. Specifically, the EAG considered optimistic and pessimistic scenarios that aligned with the 10-year and 20-year OS from the model with the upper (adjustment factor of 1.5 at 5 years) and lower (adjustment factor of 3.5 at 5 years) limits of the clinical experts' plausible ranges.[35] Furthermore, use of alternative parametric models including the loglogistic (combined with an adjustment factor of 2.5 at 5 years), which performed best in terms of AIC/BIC scores and ranked third in terms of OS extrapolations, and the stratified gamma combined with an adjustment factor of 2.5 at 5 years) which ranked second in terms of OS extrapolations were explored in the scenario analyses.

e) As mentioned earlier, for PFS all but four out of the 19 different parametric models (Gompertz, Weibull, gamma, and loglogistic) provided long-term PFS extrapolations that matched close with clinical expectations, whilst the rest of the models overestimate PFS. In their base-case analysis, the company chose the loglogistic parametric model arguing that it aligns with clinical expectations and the Committee preferences in TA742.[4] However, considering 1) the longer follow-up data from the LIBRETTO-001 trial used in this appraisal as compared to the earlier data used in TA742, 2) the visual fit to the KM data reflected in the AIC/BIC statistics which indicate that the gamma distribution would provide a better fit to the observed data as compared to the loglogistic model, and 3) the fact that the gamma distribution matches better with both

the 10-year and 20-year PFS predictions provided by the clinical experts, the EAG prefers the gamma distribution to model PFS of the *RET*-mutant MTC population in the EAG's base-case analysis. Alternative extrapolation options including the loglogistic and Weibull were explored in the EAG's scenario analyses.

4.2.6.3 Overall survival of RET fusion-positive TC

For the selpercatinib arm of the *RET* fusion-positive TC patients, 20 alternative stratified and unstratified parametric survival models were fitted to weighted OS data from the LIBRETTO-001 trial as these were generated through a naïve indirect comparison analysis. The naïve indirect treatment comparison for the *RET* fusion-positive TC patient population used data from the any-line *RET* fusion-positive TC patient population (n=65) of the LIBRETTO-001 trial, comprising of patients with patients with TC that had previously received systemic therapy (n=41) and patients with TC who were systemic therapy naïve (n=24), with data from the placebo arm of the trial. The CS noted that the placebo arm of the SELECT trial was considered appropriate due to the availability of crossover adjusted OS KM data for the placebo arm and that this approach aligned with the approaches used in TA535, TA742 and ID6132.[4, 28, 35]To model OS for BSC in the model the RPSFT-adjusted OS data for patients receiving placebo in the ITT population of the SELECT trial was used.[28]

The PH assumption for the OS of the *RET* fusion-positive TC was assessed using the log-cumulative hazard plot (Figure 11 in Appendix N), the Schoenfeld residual plots (Figure 13 in Appendix N), and the global Schoenfeld residuals test of proportional hazards resulting to a p-value of [redacted] for OS.[11] The company concluded that although the log-cumulative hazard plots are in general parallel between the two arms, the p-value (<0.05) presented for the Schoenfeld residuals test of PH indicate violation of the proportional hazards assumption for the OS for selpercatinib versus BSC (based on SELECT).

Table 4.9 summarises the AIC and BIC values for each of the OS survival models. Based on the statistical goodness of fit criteria, the log-normal, followed by the loglogistic and generalised gamma models presented the best fit to the observed KM data. From the stratified models, the stratified log-normal and stratified loglogistic models presented the best fit to the observed KM data.

Table 4.9: AIC and BIC statistics for OS parametric models for selpercatinib and BSC, *RET* fusion-positive TC

Model	AIC	Rank (AIC)	BIC	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]

Model	AIC	Rank (AIC)	BIC	Rank (BIC)
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[a]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential	[redacted]	[redacted]	[redacted]	[redacted]

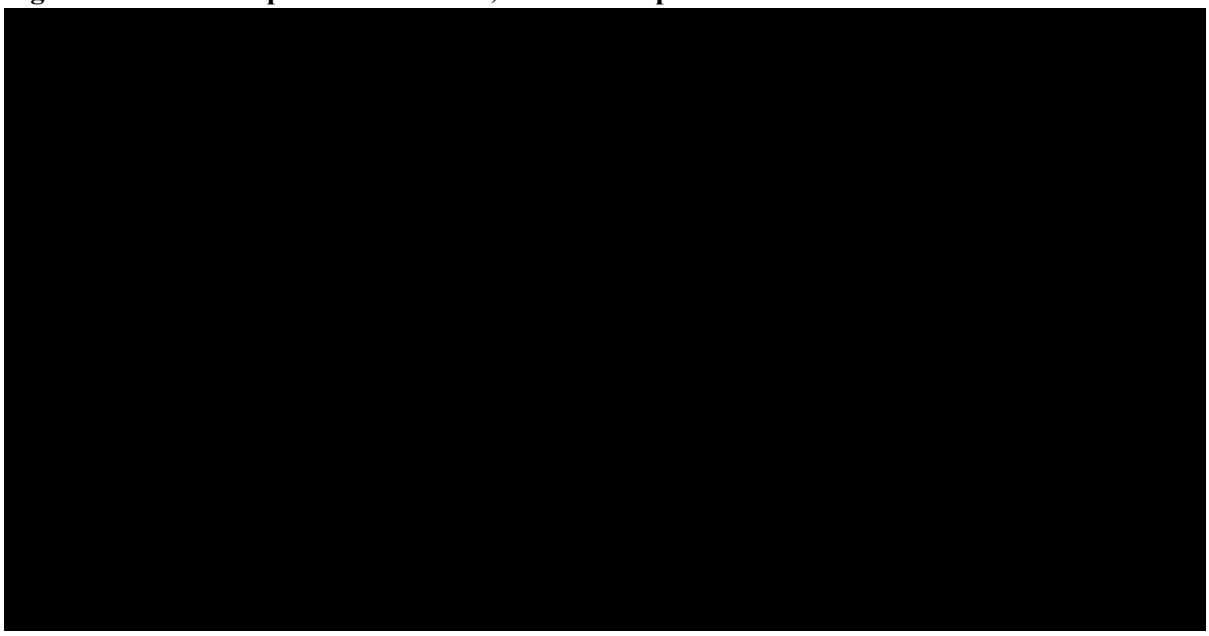
Based on Table 66 of the CS.[5]
[a]Table 66 of the CS or the text referring to the table did not comment on the reason the stratified spline/knot 3 model included NAs in the table.
AIC = Akaike information criterion; BIC = Bayesian information criterion; BSC = best supportive care; CS = company submission; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 4.5 and Figure 4.6 below present the long-term OS extrapolations as estimated based on the 20 alternative parametric models, while Table 4.10 and Table 4.11 present the corresponding median and landmark OS estimates at 5, 10 and 20 years.

Figure 4.5: OS extrapolations for selpercatinib, *RET* fusion-positive TC

Based on Figure 39 of the CS.[5]
CS = company submission; TC = thyroid cancer; OS = overall survival; Prop = proportion; *RET* = rearranged during transfection

Figure 4.6: OS Extrapolations for BSC, *RET* fusion-positive TC



Based on Figure 40 of the CS.[5]
BSC = best supportive care; CS = company submission; OS = overall survival; Prop = proportion; *RET* = rearranged during transfection; TC = thyroid cancer

The CS commented that based on AIC/BIC criteria, no models demonstrated a substantially superior statistical fit to the observed KM data. To justify the final choice of their preferred parametric function for OS extrapolations, the company used the UK clinical experts' feedback provided during the ongoing appraisal for selpercatinib in untreated, advanced thyroid cancer with *RET* alterations (ID6132).[36] Based on the experts' estimates, the company concluded that the piecewise exponential extrapolation would be the most appropriate model OS for selpercatinib and BSC, also aligning with the Committee preferences in TA742.[4] An adjustment factor of 1.2 to the OS hazard rate of the selpercatinib from five years and onwards was also implemented in the piecewise exponential model of the selpercatinib arm. The reasoning behind the adjustment was that the piecewise exponential model overestimated OS survival versus the estimates provided by the clinical experts (shown in Table 4.10 below). To model the OS of the BSC arm, the same model option was used but without the adjustment factor. The Weibull extrapolation, with the 1.2 adjustment factor applied (only for the selpercatinib arm), was explored in a scenario analysis.

Table 4.10: Median and landmark OS survival estimates for selpercatinib, *RET* fusion-positive TC

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	NA	NA	35–50	5–15
Median and landmark survival as estimated by the alternative parametric functions				
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]

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
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]
Median and landmark survival with adjustment factor applied				
Piecewise exponential (1.2 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 61 of the CS[5]
Note that parametric curves are ordered from highest to lowest 10-year survival.
CS = company submission; NA = not applicable; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

Table 4.11: Median and landmark OS survival estimates for BSC, *RET* fusion-positive TC

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	NA	5	0–2	0
Median and landmark survival as estimated by the alternative parametric functions				
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]

Models/Clinical Experts	Median OS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 62 of the CS. [5]
Note that parametric curves are ordered from highest to lowest 10-year survival.
BSC = best supportive care; CS = company submission; NA = not applicable; OS = overall survival; *RET* = rearranged during transfection; TC = thyroid cancer

EAG comments: The EAG comments on the OS of the *RET* fusion-positive TC population are presented in the end of Section 4.2.6.4 combined with the EAG comments on the PFS of the *RET* fusion-positive TC population.

4.2.6.4 Progression-free survival of RET fusion-positive TC

Similar to the OS data for the *RET* fusion-positive TC patients, various stratified and unstratified parametric functions were fitted to the PFS KM data for the any-line TC population from the LIBRETTO-001 trial and the PFS KM data for the ITT population receiving BSC in the SELECT trial (n=131).

The PH assumption for the PFS of the *RET* fusion-positive TC was assessed using the log-cumulative hazard plot (see Figure 10 in Appendix N), the Schoenfeld residual plots, (see Figure 12 in Appendix N) and the global Schoenfeld residuals test of proportional hazards resulting to a p-value of [redacted].[11] The company concluded that although the log-cumulative hazard plots illustrate parallel lines, the p-values (<0.05) presented for the Schoenfeld residuals test of PH indicate violation of the proportional hazards assumption for both the PFS and the OS for selpercatinib versus BSC (based on SELECT).

Table 4.12 summarises the AIC and BIC values for each of the 19 survival models used for the PFS analyses. Based on the statistical goodness of fit criteria, the 3-knot spline extrapolation presented the best fit to the observed PFS KM data. However, the company concluded that as all extrapolations demonstrate similar AIC/BIC criteria, clinical plausibility in terms of landmark PFS estimates was prioritised for the model selection.

Table 4.12: AIC and BIC statistics for PFS parametric models for selpercatinib and BSC, *RET* fusion-positive TC

Model	AIC	Rank (AIC)	BIC	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]

Model	AIC	Rank (AIC)	BIC	Rank (BIC)
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified spline/knot = 3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 63 of the CS.[5]

[a]Table 63 of the CS or the text referring to the table did not comment on the reason the stratified spline/knot 3 model included NAs in the table.

AIC = Akaike information criterion; BIC = Bayesian information criterion; BSC = best supportive care; CS = company submission; NA = not applicable; PFS = progression-free survival: *RET* = rearranged during transfection; TC = thyroid cancer

Figure 4.7 and Figure 4.8 below present the long-term PFS extrapolations as estimated based on the alternative parametric models, while Table 4.13 and Table 4.14 present the corresponding median and landmark PFS estimates at 5, 10 and 20 years.

Figure 4.7: PFS Extrapolations for selpercatinib, *RET* fusion-positive TC

Based on Figure 37 of the CS.[5]

CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival; Prop = proportion; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 4.8: PFS Extrapolations for BSC, *RET* fusion-positive TC

Based on Figure 38 of CS.[5]
BSC = best supportive care; CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival; Prop = proportion; *RET* = rearranged during transfection; TC = thyroid cancer

The company's preferred parametric function for PFS was primarily justified on the feedback that was provided by clinical experts during the ongoing appraisal for selpercatinib in patients with untreated, advanced thyroid cancer with *RET* alterations (ID6132) summarised in Table 4.13 below.[35] Based on this feedback it was concluded that the stratified Weibull extrapolation would be the most appropriate to model PFS for selpercatinib and BSC. This choice aligned with the Committee preferences in the original appraisal of selpercatinib in TA742.[4] The exponential extrapolation was explored in a scenario analysis.

Table 4.13: Median and landmark PFS survival estimates for selpercatinib, *RET* fusion-positive TC

Models/Clinical Experts	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	NA	[redacted]	[redacted]	[redacted]
Median and landmark survival as estimated by the alternative parametric functions				
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]

Models/Clinical Experts	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
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]

Based on Table 64 of the CS.[5]
Note that parametric curves are ordered from highest to lowest 10-year survival.
CS = company submission; NA = not applicable; PFS = progression-free survival; *RET* = rearranged during transfection; TC = thyroid cancer

Table 4.14: Median and landmark PFS survival estimates for BSC, *RET* fusion-positive TC

Models/Clinical Experts	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Landmark survival based on clinical experts				
Expectation	NA	0	0	0
Median and landmark survival as estimated by the alternative parametric functions				
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]

Models/Clinical Experts	Median PFS (months)	5-year survival (%)	10-year survival (%)	20-year survival (%)
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]

Based on Table 65 of the CS.[5]
Note that parametric curves are ordered from highest to lowest 10-year survival.
BSC = best supportive care; CS = company submission; NA = not applicable; PFS = progression-free survival; *RET* = rearranged during transfection; TC = thyroid cancer

EAG comment: Similarly to the EAG comments for the OS and PFS of the *RET*-mutant MTC population, the EAG thinks that the original concerns around the appropriateness of the data sources used to inform the survival analyses of the *RET* fusion-positive TC population in TA742 still hold in the current appraisal:[4]

a) Given the lack of comparability between the LIBRETTO-001 and the SELECT trials, the company conducted a naïve comparison for both OS and PFS data, without conducting a matching or correcting for confounding via other approaches. The EAG maintains that this approach leads to substantial uncertainty with regards to the comparative effectiveness of selpercatinib versus BSC in patients with *RET*-fusion positive TC (see also comments in Section 3.4.2).

b) To inform the OS and PFS data of the *RET* fusion-positive TC population, the company used survival data from the any-line TC patient population from the LIBRETTO-001 trial in the current appraisal. However, in TA742 the company had used the previously treated patient population (n=19) from the LIBRETTO-001 trial to inform survival of patients with *RET* fusion-positive TC receiving selpercatinib throughout the assessment (clarification question B1).[1] This change had not been requested by the EAG or the Committee in TA742.[4] The company justified this change firstly referring to consistency given that the SELECT trial only provided the PFS KM data for a pre-treated population while the OS KM data were not available for pre-treated patients separately. The company went further on commenting that *"furthermore, a comparison between the prior systemic therapy RET fusion-positive TC population in the LIBRETTO-001 trial and the any-line ITT population receiving placebo in the SELECT trial is anticipated to introduce bias against selpercatinib, with clinical experts consulted as part of TA742 supporting that prior treatment may be considered a prognostic factor for these patients."*[1] Although the EAG agrees with the company that including survival data for a mixed population (consisting of naïve and previously treated patients) for both selpercatinib and BSC arms, may reduce potential bias, it still remains inconsistent with the population of interest in this appraisal, consisting of only previously treated patients.

   The EAG's concerns are strengthened by the fact that OS and PFS for the *RET* fusion-positive TC population are substantially lower for previously treated patients than for naïve patients as shown in Table 1.7 of the CSR.[14] The request by the EAG to provide a scenario analysis in which the survival data for selpercatinib are informed from the previously treated patients was declined by the company arguing that such an analysis is expected to substantially bias results against selpercatinib (clarification question B3).[1] The company substantiated this response by adding the

proportion of patients with TC that had not received prior MKI/TKI therapy in the LIBRETTO-001 trial ([redacted] against the respective proportion in the placebo arm of the SELECT (79.4%) trials (question B3d). Furthermore, as summarised in the EAG comments of Section 3.4.2, the company further conducted an ITC for PFS using the pre-treated population, showing that the results were largely consistent with those for the whole population i.e., PFS HR [95% CI] of [redacted] instead of [redacted]) (clarification response A16).[1] However, as also highlighted in Section 3.4.2, although these results provide some levels of confidence that line of treatment may not be an effect modifier, they cannot lead to any firm conclusions regarding the absolute OS per treatment arm and do not offset the lack of comparability between the trials. The EAG concurs with the company's perspective that using the 'prior lenvatinib/sorafenib' *RET* fusion-positive TC population of the LIBRETTO-001 trial and the any-line *RET*-mutant placebo arm of the SELECT trial would be associated with a bias against selpercatinib. However, considering the existing uncertainties around the comparability of the populations between the two trials, the EAG thinks such an analysis would still be informative, representing a lower bound of survival gains for selpercatinib against BSC.

c) It is unclear to the EAG why the company has used a different set of parametric models for each survival analysis throughout the CS. Specifically, the company used 19 parametric models to inform the OS and PFS of the *RET*-mutant MTC population and the PFS of the *RET*-fusion positive TC population, whilst they also fitted a piecewise exponential model for the OS of the *RET* fusion-positive TC population (20 in total). Furthermore, regarding the OS of the *RET* fusion-positive TC population, Table 4.10 and Table 4.11 as well as the electronic model include 17 different parametric models, with the stratified spline 1/2/3 knot models missing, while those are still part of Table 4.9 where the AIC/BIC scores for all 20 models are reported.

d) The CS argued that to align with the input from the clinical experts for the OS of the *RET* fusion-positive TC patient population, the piecewise exponential model was selected due to the long-term OS estimates that matched closer to the ranges provided by the clinical experts. However, following the company's response to clarification question B3e in which a reporting error was pointed out by the EAG for the piecewise exponential model values, Table 4.10 above shows that the piecewise exponential model does not lead to 10- and 20-year OS predictions that match closer to the ranges provided by the clinical experts. In response to clarification question B3a, the company stated that "*when assessing OS extrapolations explored for selpercatinib in the RET fusion-positive TC population, it was found that all curves that predicted survival rates within clinical expert estimates at 10 years overestimated survival at 20 years. Similarly, the two curves that predicted survival rates within clinical expert estimates at 20 years underestimated survival at 10 years"*.[1] The company went on in their response mentioning that, as none of the survival extrapolations for the OS of selpercatinib produce clinically plausible estimates at all timepoints provided by clinical experts during validation to support the first-line thyroid submission for selpercatinib (ID6132), the piecewise exponential extrapolation was chosen for this population in recognition of Committee preferences in TA742.[1] The EAG does not concur with the company's approach to selecting the parametric function of OS and finds the company's rationale here inconsistent and contradictory to the approach stated to be taken for the selection of the OS/PFS survival functions in the *RET* mutant MTC population. The piecewise exponential model for the OS of the *RET* fusion-positive TC population seems to be selected only because it coincided with the Committee's preference in TA742.[4] However, such an approach also disregards the longer follow-up data of the LIBRETTO-001 trial. Based on the clinical plausibility criterion the stratified gamma or stratified Weibull would get closer to the estimates provided by the clinical experts for selpercatinib and BSC, without the

need to implement adjustment factors for selpercatinib (Table 4.10 above). Also, in terms of AIC criteria these two model options are not different than the piecewise exponential while they rank only slightly worse in terms of BIC criteria. Therefore, the EAG selected the stratified gamma for the base-case analysis of the *RET* fusion-positive TC population, while use of the stratified Weibull was explored in the scenario analysis. Finally, to address the uncertainties around the implementation of the adjustment approach for the OS of selpercatinib arm, the EAG has followed the EAG's approach during the appraisal for selpercatinib in patients with untreated, advanced thyroid cancer with *RET* alterations (ID6132),[4] and has run additional scenarios in which the adjustment factor for the piecewise exponential model was varied. Specifically, the EAG considered optimistic and pessimistic scenarios that aligned with the 10-year and 20-year OS survival from the model with the upper (adjustment factor of 0.9 at 60 months) and lower (adjustment factor of 1.5 at 18 months) limits of the clinical experts' plausible range.

e) For the PFS of the *RET* fusion-positive TC population, the company's preferred parametric function is the stratified Weibull model primarily justified on the feedback that was provided by clinical experts during the ongoing appraisal for selpercatinib in patients with untreated, advanced thyroid cancer with *RET* alterations (ID6132),[4] while the exponential extrapolation was explored in a scenario analysis. The EAG concurs with the company's selected curves for the PFS.

4.2.6.5 Time to treatment discontinuation

Time to treatment discontinuation (TTD) in the selpercatinib arm, for both the *RET*-mutant MTC and *RET* fusion-positive TC populations, was set equal to PFS, with the addition of the mean time from progression to treatment discontinuation, as observed in the previously treated *RET*-mutant MTC and the previously treated *RET* fusion-positive TC populations ([redacted] for MTC and [redacted] for TC). That is because progressed patients in the LIBRETTO-001 trial could continue to receive selpercatinib when the patient was deriving clinical benefit from continuing the treatment.[14] UK clinical experts also confirmed that some patients may continue receiving selpercatinib beyond progression in the absence of subsequent treatments routinely available in UK clinical practice.[36]

For BSC, TTD is not considered in the economic model, as there are no specific costs associated with BSC beyond the palliative care and monitoring costs.

EAG comment: TTD was assumed equal to PFS, with the addition of the mean time from progression to treatment discontinuation, as observed in the previously treated patients of the LIBRETTO-001 trial. The CS argued that this approach aligned with the EAG's preferred approach in TA742.[4] However, the EAG in the original appraisal preferred that approach as fitting a curve based on TTD data from the earlier data cut of the trial yielded implausible TTD curves. At this point in time, with more TTD data having become available, the model fit to the updated TTD data should be re-assessed. In response to question B5, the company clarified that the updated TTD trial data with alternative extrapolation options were included in the electronic model but did not provide a complete assessment of the parametric models and plausibility of outcomes. The company clarified that they did not incorporate in the economic analysis the TTD data from the LIBRETTO-001 for consistency between this submission and ID6132, which also employed similar assumptions for TTD.[1] The EAG assessed the impact of using alternative extrapolation options for the TTD data and concluded that for the *RET*-mutant MTC population the same issue pertains as in the original appraisal: the alternative TTD extrapolation options lead to clinically implausible outcomes when compared to the PFS curves selected (loglogistic or gamma) for extrapolation. For the *RET* fusion-positive TC population, as in TA742,[4] the Weibull and gamma distributions resulted in estimated curves for *RET* fusion-positive TC that would be deemed plausible in comparison to the stratified Weibull PFS curve, but the differences with the company's

approach would be small. Therefore, the EAG concurs with the company's approach of modelling TTD data.

4.2.7 Adverse events

The company included grade ≥3 adverse events with at least 2% difference in frequency between interventions in the model. For the *RET*-mutant MTC population, the probabilities of AEs for selpercatinib were based on the MTC SAS of the LIBRETTO-001 trial (n=324) whereas probabilities of AEs for BSC were taken from the EXAM trial (n=109).[9, 17] For the *RET* fusion-positive population probabilities were used from TC safety analysis set of the LIBRETTO-001 trial (n=66) and from the placebo arm of SELECT (n=131).[10]

Adverse events incidences for patients with *RET*-mutant MTC and *RET* fusion-positive TC are displayed in Tables 71 and 72 of the CS respectively.

EAG comment: Some of the AEs included in Tables 71 and 72 of the CS and in the model, did in fact not vary by at least 2% between selpercatinib and BSC and thus should not be included, based on the inclusion rule the company had defined. When asked about this in the clarification letter (Question B6),[1] the company explained that as the model contains other comparators as well, the rule of at least 2% difference might have been between selpercatinib and another comparator. The company adjusted the model such that indeed only AEs are now included for which the frequency was at least 2%. Tables 4.15 and 4.16 show the incidences of all included AEs.

It should be noted that no adjustments were made for AEs to correct for potential confounders, so this represents a naïve comparison between selpercatinib and placebo in the two included populations. It is unclear how differences in the study populations would have affected AE results, but the AE incidence has only a negligible impact on the overall costs and quality-adjusted life years (QALYs) and hence on the ICER.

Table 4.15: Incidence of Grade 3 or 4 adverse events included in the model for the *RET*-mutant MTC population

Adverse event	Selpercatinib (n=324)	BSC (n=109)
Diarrhoea	6.79%	1.83%
Hypertension	21.60%	0.00%
ECG QT prolonged	[redacted]	0.00%
Abdominal pain	3.09%	0.92%
Haemorrhage	[redacted]	0.92%
Back pain	[redacted]	0.92%
Alanine aminotransferase increased	8.95%	1.83%
Aspartate aminotransferase increased	7.72%	0.00%
Hyponatraemia	[redacted]	0.00%
Lymphopenia	[redacted]	10.09%
Pneumonia	[redacted]	0.00%
Dehydration	[redacted]	0.00%
Weight increased	[redacted]	0.00%
Ascites	[redacted]	0.00%
Sepsis	[redacted]	0.00%

Adverse event	Selpercatinib (n=324)	BSC (n=109)
Hyperkalaemia	[redacted]	0.00%
Hypophosphatemia	[redacted]	0.00%
Hyperglycaemia	[redacted]	0.00%
Hypercalcemia	[redacted]	0.00%
Source	LIBRETTO-001, MTC safety analysis set (n=324)	EXAM[9, 17]
BSC = best supportive care; ECG = electrocardiogram; MTC= medullary thyroid cancer; *RET* = rearranged during transfection		

Table 4.16: Incidence of Grade 3 or 4 adverse events included in the model for the *RET* fusion-positive TC population

Adverse event	Selpercatinib (n=66)	BSC (n=131)
Diarrhoea	7.58%	0.00%
Hypertension	15.15%	3.82%
ECG QT prolonged	[redacted]	0.00%
Abdominal pain	[redacted]	0.00%
Sepsis	[redacted]	0.00%
Hyponatraemia	[redacted]	0.00%
Vomiting	[redacted]	0.00%
Back pain	3.03%	0.00%
Hypophosphatemia	[redacted]	0.00%
Alanine aminotransferase increased	[redacted]	0.00%
Aspartate aminotransferase increased	[redacted]	0.00%
Thrombocytopenia	[redacted]	0.00%
Lymphopenia	[redacted]	0.00%
Pneumonia	[redacted]	0.00%
Anaemia	[redacted]	0.00%
Hypokalaemia	[redacted]	0.00%
Leukopenia	[redacted]	0.00%
Neutropenia	[redacted]	0.00%
Confused state	[redacted]	0.00%
Source	LIBRETTO-001, TC safety analysis set (n=66)[redacted]	SELECT[28]
BSC = best supportive care; ECG = electrocardiogram; *RET* = rearranged during transfection; TC = thyroid cancer		

4.2.8 Health-related quality of life

Utility values were estimated for the PF and PD health state. HRQoL data were collected in the LIBRETTO-001 study using the EORTC QLQ-C30. The questionnaires were answered on the first day of treatment, at the start of each 4-week treatment cycle (within seven days of each radiologic assessment, preferably before the results of the assessment were known), and at the end of the treatment visit. Consequently, there were limited data collected for patients that had progressed. The LIBRETTO-001 trial did not collect European Quality of Life-5 Dimensions (EQ-5D) data.

4.2.8.1 Health-related quality of life data identified in the systematic literature review

According to the CS, the SLR did not identify HRQoL studies specific to patients with *RET*-mutant MTC or *RET* fusion-positive TC. Table 40 of appendix H of the CS, provides an overview of the four published HRQoL studies identified in the economic SLR, but those were not selected by the company for the economic model as they did not provide utility estimates relevant to the population and health states of the current model. The company also examined the SLR of NICE TA928, but was not able to identify additional relevant HRQoL or utility data.[37]

EAG comment: The SLR for HRQoL was performed in August 2019 for TA742, and no effort was made to include more recent HRQoL studies through a new SLR. When asked to provide such an update during clarification, the company declined this request. The EAG found in a quick search 741 studies published since August 2019. An incomplete (due to time constraints) screening of title and abstract already identified two potentially relevant papers, i.e., a mapping study by Huang et al (2024) that was done in patients with papillary thyroid carcinoma,[24] and a systematic review by Houten in 2021.[25] It is possible that other studies might have been identified if a proper update of the SLR had been performed.

4.2.8.2 Mapping the EORTC data

The company stated that in previous submission TA742, the HRQoL data from the LIBERTTO-001 study was mapped to EQ-5D using an algorithm from Kahn et al.[38] This mapping gave highly implausible results (mean utilities > [redacted] for pre- and post-progression in all subgroups).[4] Therefore, in TA742,[4] the values used in TA516[27] and TA535[28] which were sourced from a vignette study conducted by Fordham et al (2015) were used.[26] These utilities were estimated as 0.80 for progression-free patients and 0.50 for progressed patients.

For the current submission, the company used the EORTC-QLQ-C30 data from the any-line *RET*-altered TC and MTC populations, from the 13th January 2023 DCO of LIBRETTO-001, 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).[39-41] These results are presented in Table 4.17

Table 4.17: Mapping of EORTC-QLQ-C30 data from LIBERTTO-001 to estimate EQ-5D utilities

Source	Progression-free (SD)	Progressed (SD)
LIBRETTO-001 EORTC data for *RET*-mutant MTC any-line		
EORTC-8D	[redacted]	[redacted]
Mapped to EQ-5D (Young, 2015) [39]	[redacted]	[redacted]
Mapped to EQ-5D (Kontodimopoulos, 2009)[40]	[redacted]	[redacted]
Mapped to EQ-5D (Marriott, 2017)[41]	[redacted]	[redacted]
LIBRETTO-001 EORTC data for *RET* fusion-positive TC any-line		
EORTC-8D	[redacted]	[redacted]
Mapped to EQ-5D (Young, 2015) [39]	[redacted]	[redacted]
Mapped to EQ-5D (Kontodimopoulos, 2009)[40]	[redacted]	[redacted]

Source	Progression-free (SD)	Progressed (SD)
Mapped to EQ-5D (Marriott, 2017)[41]	[redacted]	[redacted]

Based on Table 73 of the CS.[5]
CS = company submission; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life-5 Dimensions; MTC = medullary thyroid cancer; N = number of patients; n = number of assessments; *RET* = rearranged during transfection; SD = standard deviation; TC = thyroid cancer

Based on these results, the company concluded in the CS that in both the any-line MTC and TC populations, the mapped utility estimates seem implausible. For the *RET*-mutant MTC population, regardless of the mapping method, the mapped mean utility values for progressed disease are higher compared to those in progression-free. In the *RET* fusion-positive TC population, the company argued that the mapped utilities come with a high uncertainty due to a small patient number and number of assessments, especially in the progressed state [redacted] and that the results do not reflect the anticipate loss in HRQoL associated with disease progression.

Therefore, in the CS, the company decided to use the Fordham et al values for the base-case model.[26] However, in response to the clarification letter (question B9),[1] the company indicated that utility values were updated to the utility values mapped from EORTC-QLQ-C30 data collected from the any-line *RET* fusion-positive TC population for the LIBERTTO-001 trial using the Young mapping algorithm (see Table 4.18).[39] This change is in line with the Committee preferences for the ongoing appraisal for selpercatinib in the first-line thyroid indication (ID6132).[42]

Table 4.18: Health state utility values weights as used in the economic model

Health state	Utility value (SD)	Reference	Justification
Progression-free	[redacted]	LIBRETTO-001 EORTC mapped to EQ-5D (Young 2015)[43]	LIBRETTO-001 EORTC data for *RET* fusion-positive TC
Progressed	[redacted]		

Based on Table 50 of the response to the clarification letter.[1]
EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life-5 Dimensions; SD = standard deviation; TC = thyroid cancer

EAG comment: The EAG has some concerns regarding the selection of utility values for the progression-free and progressed health states:

a) Two of the included mapping algorithms applied by the company are those that the EAG had identified in TA742, and all were published before 2019 (year of SLR TA742). As mentioned in Section 4.2.8.1, the EAG therefore asked the company during clarification if any effort had been made to identify more recent studies for the mapping algorithms. The EAG had found with a quick scan of the literature one more recently published mapping study that could potentially be useful.[24] Unfortunately, the company did not see a need for an update of the SLR and further did not respond on whether the study found by the EAG could be of use or not. Given the implausible results for the *RET*-mutant MTC population, it might be worth exploring what utility estimates would follow from this alternative algorithm, even though it was developed in a Chinese population with a Chinese value set for the EQ-5D utilities.
b) Whilst the EAG understands the request of NICE to the company to follow the Committee preferences for the ongoing appraisal for selpercatinib in first-line (ID6132), they are concerned about the extremely small sample size available in the *RET* fusion-positive TC any-line group

post-progression, i.e., [redacted]. In the *RET*-mutant MTC group on the other hand [redacted] were available, so not only more patients but also more assessments per patient. In that light, it seems relevant to explore possible explanations why these implausible post-progression utilities are observed. For example, as discussed earlier, some patients continue treatment after progression, and it would be of interest to know if any of these patients are among those [redacted] with post-progression assessments. In addition, it may be possible that in the populations of this appraisal, the decline in HRQoL is very slow. In that regard, it would be of interest to know for each of the patients at which time point post-progression the questionnaire was administered.
Nevertheless, the EAG does agree with the use of the more conservative set of utilities for the base-case analysis.

4.2.8.3 Disutility values adverse events

Disutility values for Grade 3 and 4 adverse events were applied to those experiencing AEs to estimate the reduction in quality of life. For the *RET*-mutant MTC group, the same utility decrement was assumed for all AE based on a study from Beusterien et al 2009,[44] and, in line with TA516,[27] a duration of one month was assumed. For the *RET* fusion positive TC population, specific disutilities for diarrhoea and fatigue were based on TA535.[28] The utility decrements of AEs are presented in Table 4.19.

EAG comment: The difference between the utility decrement in patients with diarrhoea of patients with *RET*-mutant MTC versus *RET* fusion-positive TC appears disproportionate and lacks face validity. However, the impact of this estimate on the ICER is negligible.

Table 4.19: Utility decrements for Grade 3 or 4 adverse events included in the model for both the *RET*-mutant MTC population and the *RET* fusion-positive TC population

Adverse events	Utility Decrement		Duration (days)	Sources
	***RET*-mutant MTC**	***RET* fusion-positive TC**		
Diarrhoea	-0.110	-0.380	30.4	TA516 TA535 (TC utilities)
Fatigue	-0.110	-0.080		
All other AE	-0.110			

Based on table 74 and 75 of the CS.[5]
AE = adverse event; CS = company submission; MTC = medullary thyroid cancer; *RET* = rearranged during transfection; TC = thyroid cancer

4.2.8.4 Age-adjustment utilities

As people age, their utility is expected to decrease. Since the model uses a lifetime horizon, an annual adjustment factor for age is included. This factor, derived from Ara and Brazier et al (2010),[45] is applied to the health state utilities using a multiplicative approach.

EAG comment: In line with the NICE Manual,[31] the company has adjusted utilities for age using a multiplicative approach, based on a model from the publication of Ara and Brazier et al(2010),[45] which uses Health Survey for England data (HSE) from 2003 and 2006. For consistency between the previous NICE submission for thyroid cancer, the EAG acknowledges the choice of the company to use this method from Ara and Brazier et al. 2010.[45] However, recent work by Hernández et al recommend to use *"the most up to date information available that has direct observation of EQ-5D-3L from the HSE*".[46] Based on that publication, the latest available HSE including EQ-5D-3L data is the collected

in 2014. Though the EAG would have preferred the use of these HSE 2014 based age-dependent utilities, the impact on the ICER of such adjustment is negligible.

Furthermore, the EAG noticed a small programming error in Excel for the *RET*-mutant MTC population, as in the calculation of the age-adjusted utilities the age and %female from the *RET* fusion-positive TC population is used. The impact of this on the outcomes is minimal.

4.2.9 Resources and costs

The cost components included in the model are drug acquisition costs for selpercatinib, the associated costs of administrating the drug and monitoring costs, health state costs, cost of BSC, costs associated with the management of AEs, and costs of end-of-life palliative care.

4.2.9.1 Treatment costs (with PAS)

4.2.9.1.1 Drug acquisition costs

Selpercatinib is provided as a Patient Access Scheme (PAS) discount of [redacted] on the list price of [redacted] per pack for 40 mg, and [redacted] for 80 mg, respectively. The list prices for selpercatinib are sourced from the British National Formulary (BNF).[47] The licensed dose for selpercatinib is 160 mg, orally, twice daily.[47] Table 4.20 shows the drug acquisition cost for selpercatinib included in the cost-effectiveness analysis. The total costs for selpercatinib were derived by applying the cost of the drug to the modelled time to discontinuation.

Table 4.20: Drug acquisition costs for selpercatinib

Regimen	Strength/unit	Pack size	Cost per pack (list)	Cost per pack (PAS)	Source
Selpercatinib	80 mg	112	£8,736.00	[redacted]	BNF[47]
	40 mg	168	£6,552.00	[redacted]	BNF[47]
Based on Based on Table 77 in CS.[5] BNF = British National Formulary; CS = company submission; PAS = Patient Access Scheme					

In the model the proportion of selpercatinib administrations at each dose level was based on the recorded doses received from the LIBRETTO-001 trial, which was adjusted to reflect the available tablet sizes of 40 mg, and 80 mg. In the first treatment period in the model (four weeks) no dose reductions were applied. In the subsequent treatment periods of four weeks each, in order to account for selpercatinib dose reductions, proportions of patients were assumed to have received a dose level of 20 mg to 160 mg orally, twice daily. The proportion of patients receiving each dose of selpercatinib by treatment period in the model is shown in Table 4.21. In the first period, the cost per week is £708.68, totalling £2,834.71 for four weeks. For MTC, in the subsequent treatment periods, the cost per week is [redacted], totalling [redacted] for four weeks. For TC, in the subsequent treatment periods, the cost per week is [redacted], totalling [redacted] for four weeks.

Table 4.21: 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 (%)*
First treatment period		
160	[redacted]	[redacted]
120	[redacted]	[redacted]
80	[redacted]	[redacted]
Subsequent treatment periods		
160	[redacted]	[redacted]
120	[redacted]	[redacted]
80	[redacted]	[redacted]
60	[redacted]	[redacted]
40	[redacted]	[redacted]
20	[redacted]	[redacted]

* We present the % used in the model based on the electronic version of the model (adjusted for whole tablets and rounding errors)
mg = milligram; MTC = medullary thyroid cancer; NA = not applicable; *RET* = rearranged during transfection; TC = thyroid cancer

4.2.9.1.2 Administration and monitoring

In the CS it is stated that in line with TA520 administration costs consisting of 12 minutes of pharmacy time every 30 days was assumed for selpercatinib (£11.40).[48] Inspection of the Excel model, though, showed that these pharmacy costs are applied per four weeks, i.e., 28 days. As part of monitoring costs, seven electrocardiograms (ECGs) would be required, one after the first week of treatment followed by one every month for six months.[49] The cost per ECG amount to £159.36 (code EY51Z NHS reference costs (2021/22).[50]

4.2.9.1.3 RET testing costs

In the CS, the company explains that *RET* rearrangements are routinely tested alongside other oncogenic drivers in a standardised way across different centres.[51, 52] Thus, they do not anticipate that approval of selpercatinib will lead to additional costs to the NHS due to specific screening for *RET* alterations.

Nevertheless, the company has included the costs of testing into the base-case analyses. The cost of *RET* testing (£34) was included,[53] combined with a screen-positive rate of 61.2% for *RET*-mutant MTC and of 6.8% for *RET* fusion-positive TC.[54-56]

4.2.9.2 Health state costs

Unit costs and resource use per year in *RET*-mutant MTC and *RET*-fusion positive TC populations is presented in Table 4.22. Resource use for the *RET*-mutant MTC and *RET*-fusion positive TC is assumed to be the same in the base-case. For best supportive care, which was assumed to consist of monitoring and palliative care, the resource use of the progression-free health state was assumed to be the same as for the progressed health state.

Table 4.22: Unit costs and resource use by health state per year

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, computerised tomography scan of more than 3 areas RD27Z
Source resource use: NICE TA516 CT = computed tomography; NHS =National Health Service; PD = progressed disease; PF = progression-free				

The costs associated with palliative care (£10,676.25)[27, 48] and palliative chemotherapy (£1,016.14)[50] that are expected to occur near the end of life were applied at the point of death to all patients.

Since there are no subsequent treatments available following treatment with second-line selpercatinib or best supportive care, following disease progression, patients were assumed to receive no active subsequent treatments.

4.2.9.3 Adverse event costs

Unit costs for adverse events for the *RET*-mutant MTC and *RET* fusion-positive TC populations are shown in Table 4.23.

Table 4.23: Adverse event unit costs for the *RET*-mutant MTC and *RET* fusion-positive TC populations

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)
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

Adverse event	Mean cost per episode (£)	Source
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)
Decreased appetite	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)
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)
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
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)
Vomiting	3043.95	NHS Reference costs 2021/22; Assumption (FD04E Nutritional Disorders without Interventions with CC Score 0-1 Non-Elective Inpatient)
All other AEs	0.00	Assumption
Based on Based on Table 82 and 83 in CS.[5] AE = adverse event; CS = company submission; ECG = electrocardiogram; MTC = medullary thyroid cancer; NHS =National Health Service; *RET* = rearranged during transfection; TC = thyroid cancer		

4.2.10 Severity

The NICE reference case stipulates that the Committee will regard all QALYs as being of equal weight. The Committee may also consider the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier. Severity can be then taken into account quantitatively in cost effectiveness analyses through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.24. The calculation option that implies the greater severity level will be considered, and if either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.[31]

Table 4.24: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality adjusted life year		

The results of the QALY shortfall analysis are shown in Table 4.25, where the total lifetime QALYs associated with BSC were obtained from the base-case analysis results, and the estimated total QALYs for the general population reflecting the baseline characteristics of the LIBRETTO-001 trial for the *RET*-mutant MTC population (39.0% female and [redacted] years) and the *RET* fusion-positive TC population (50.8% female and [redacted] years). These results suggest that a QALY weight of 1.2 can be applied.

Table 4.25: Summary of company QALY shortfall analysis

Expected total QALYs for the general population	Total expected QALYs for people with BSC	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
***RET*-mutant MTC**				
14.02	1.51	12.51	89.23%	1.2
***RET* fusion-positive TC**				
13.39	1.27	12.12	90.51%	1.2
Based on Table 86 of the CS[5] BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; *RET* = rearranged during transfection; QALY = quality-adjusted life year; TC = thyroid cancer				

EAG comment: The QALY shortfall results presented in Table 4.25 were validated by the EAG. In addition, the Institute for Medical Technology Assessment Disease Burden Calculator (iDBC) tool also estimates the likelihood of the applicable QALY weight based on the probabilistic sensitivity analysis (PSA) results provided in the company's model, which can be used to estimate the severity adjusted probability of being cost-effective.[57] The QALY shortfall calculations conducted by the EAG were broadly in line with those presented by the company. The uncertainty around the QALY weights shows that for the *RET*-mutant MTC population even though the weighted point estimate is 1.2, there is a 40% probability that the applicable QALY weight is 1.0, and a 15.0% probability that the applicable QALY weight is 1.7, which may have an impact on the severity adjusted results. The uncertainty around the QALY weights shows that for the *RET* fusion-positive TC population even though a weighted point estimate is 1.2, there is a 19% probability that the applicable QALY weight is 1.0, and a 14.0% probability that the applicable QALY weight is 1.7, which may have an impact on the severity adjusted results.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

5.1.1 Main results original company submission

In Section B.3.10 of the CS,[5] the company presented their cost effectiveness results by reporting both the probabilistic ICERs and incremental net health benefit, using the PAS price for selpercatinib, while the deterministic and disaggregated results were presented in Appendix J of the CS.[11] To make this section more concise, the EAG only presents the deterministic and disaggregated results.

Table 5.1 shows the company's deterministic base-case results for selpercatinib compared to BSC. All results are discounted. For the *RET*-mutant MTC population results indicated that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (incremental cost of [redacted]) than BSC amounting to an ICER of £47,681 per QALY gained. For the *RET* fusion-positive TC population results indicated that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (incremental cost of [redacted]) than BSC amounting to an ICER of £45,047 per QALY gained. These results account do not account for a disease severity weight in the QALY calculations of both populations. Disaggregated discounted QALYs and costs are shown in Tables 5.2 and 5.3, respectively.

Table 5.1: Company's base-case deterministic cost effectiveness results (selpercatinib PAS price), original submission

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
***RET*-mutant MTC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,681
BSC	17,085	2.67	1.51				
***RET* fusion-positive TC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,047
BSC	16,030	2.31	1.27				

Based on Table 49 and Table 51 of the Appendix J.[11]
BSC = best supportive care; ICER = incremental cost-effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; PAS = Patient Access Scheme; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer

Table 5.2: Disaggregated QALYs results (discounted)

Health state	QALY selpercatinib	QALY BSC	Increment	Absolute increment	(%) Absolute increment
***RET*-mutant MTC**					
Progression-free	[redacted]	0.511	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	0.996	[redacted]	[redacted]	[redacted]
Total	[redacted]	**1.508**	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**					
Progression-free	[redacted]	0.351	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	0.921	[redacted]	[redacted]	[redacted]
Total	[redacted]	**1.272**	[redacted]	[redacted]	[redacted]

Health state	QALY selpercatinib	QALY BSC	Increment	Absolute increment	(%) Absolute increment
Based on Table 43 and Table 46 in Appendix J of the CS.[11] BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; *RET* = rearranged during transfection; QALY = quality-adjusted life year; TC = thyroid cancer;					

Table 5.3: Disaggregated cost results (selpercatinib PAS price, discounted)

Cost item	Cost selpercatinib (£)	Cost BSC (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
***RET*-mutant MTC**					
Drug acquisition	[redacted]	0	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	0	[redacted]	[redacted]	[redacted]
Drug monitoring	[redacted]	0	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	625	[redacted]	[redacted]	[redacted]
Diagnostic tests	[redacted]	0	[redacted]	[redacted]	[redacted]
Disease management PF	[redacted]	1,414	[redacted]	[redacted]	[redacted]
Disease management PD	[redacted]	4,430	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	10,616	[redacted]	[redacted]	[redacted]
Total	[redacted]	**17,085**	[redacted]	[redacted]	[redacted]
***RET* fusion-positive TC**					
Drug acquisition	[redacted]	0	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	0	[redacted]	[redacted]	[redacted]
Drug monitoring	[redacted]	0	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	220	[redacted]	[redacted]	[redacted]
Diagnostic tests	[redacted]	0	[redacted]	[redacted]	[redacted]
Disease management PF	[redacted]	966	[redacted]	[redacted]	[redacted]
Disease management PD	[redacted]	4,078	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	10,765	[redacted]	[redacted]	[redacted]
Total	[redacted]	**16,030**	[redacted]	[redacted]	[redacted]
Based on Table 45 and Table 48 in Appendix J of the CS.[11] BSC = best supportive care; CS = company submission; MTC = medullary thyroid cancer; PAS = Patient Access Scheme; PD = progressed disease; PF = progression-free; *RET* = rearranged during transfection; TC = thyroid cancer;					

5.1.2 Main results of the company after the request for clarification

Table 5.4 shows the deterministic cost effectiveness results of the updated company's base-case analysis (i.e., as provided alongside their response to request for clarification).[1] The updated company results accounted for disease severity, considering a QALY weight of 1.2 in both populations. To facilitate the comparison between the original and the updated results, the EAG presented both the

severity-adjusted (using parentheses) and unadjusted values in Table 5.4. For the *RET*-mutant MTC population results indicated that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (incremental cost of [redacted]) than BSC amounting to an ICER of £47,971 per QALY gained (without severity adjustment in QALYs). For the *RET* fusion-positive TC population results indicated that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (incremental cost of [redacted]) than BSC amounting to an ICER of £43,567 per QALY gained (without severity adjustment in QALY).

Table 5.4: Company's base-case deterministic cost effectiveness results (selpercatinib PAS price), after clarification

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
***RET*-mutant MTC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,971 (39,976)
BSC	16,557	2.67	1.91	-			
***RET* fusion-positive TC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,567 (36,306)
BSC	15,898	2.31	1.65	-			

Based on Table 51 and Table 53 in response to clarification questions and the electronic model following the clarification phase.[1, 2]
*Values in the parenthesis account for a QALY weight of 1.2 in both populations.
BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; MTC = medullary thyroid cancer; PAS = Patient Access Scheme; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer

EAG comments: As explained in the EAG comments in Section 4.2.5, the original company results (presented in Section 5.1.1) were produced using a 25-year time horizon, whilst the CS reported to be using a 35-year time horizon. In response to the EAG's question on this matter in B2, the company confirmed that "*the updated cost-effectiveness results presented throughout this clarification questions response continue to be based on a 35-year time horizon*".[1] The EAG confirmed the company has been using a 35-year time horizon for the updated results for the *RET* fusion-positive TC population. However, for the *RET*-mutant MTC population, the EAG confirmed that the updated company results presented in Table 5.4 above were still based on a 25-year time horizon. Therefore, the EAG corrected this error by using a 35-year time horizon and the updated results are presented in Table 5.5 below.

Table 5.5: Company's base-case deterministic cost effectiveness results (selpercatinib PAS price), after clarification and EAG correction

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
***RET*-mutant MTC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,078 (40,065)
BSC	16,562	2.67	1.91	-			

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
***RET* fusion-positive TC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,567 (36,306)
BSC	15,898	2.31	1.65	-			
Based on Table 51 and Table 53 in response to clarification questions and the electronic model following the clarification phase.[1, 2] *Values in the parenthesis account for a QALY weight of 1.2 in both populations. BSC = best supportive care; EAG = External Assessment Group; 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; TC = thyroid cancer;							

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis (PSA)

The company conducted a PSA in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 1,000 iterations. The input parameters and the probability distributions used in the PSA can be found in the "Variables - MTC" and "Variables - TC" sheets of the economic model.[2] The average PSA results are summarised in Table 5.6 and are overall in line with the deterministic ones shown in Table 5.5.

Table 5.6: Company's base-case probabilistic cost effectiveness results (selpercatinib PAS price), after clarification

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
***RET*-mutant MTC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,313
BSC	16,530	2.67	1.91				
***RET* fusion-positive TC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,851
BSC	15,871	2.31	1.65				
Based on the electronic model following the clarification phase.[1, 2] 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; TC = thyroid cancer							

The company also plotted the PSA outcomes on a cost effectiveness (CE) plane. These are shown in Figure 5.1 and Figure 5.2 for the *RET*-mutant MTC and the *RET* fusion-positive TC populations, respectively. It can be seen that [redacted]. From the PSA results, cost effectiveness acceptability curves (CEAC) were also calculated and shown in Figure 5.3 and Figure 5.4. The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that

selpercatinib is cost effective as compared to BSC was [redacted] for the *RET*-mutant MTC patient population and [redacted] for the *RET* fusion-positive TC patient population.

Figure 5.1: PSA CE-plane (selpercatinib PAS price, discounted), *RET*-mutant MTC

Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; CE = cost effectiveness; MTC = medullary thyroid cancer; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection

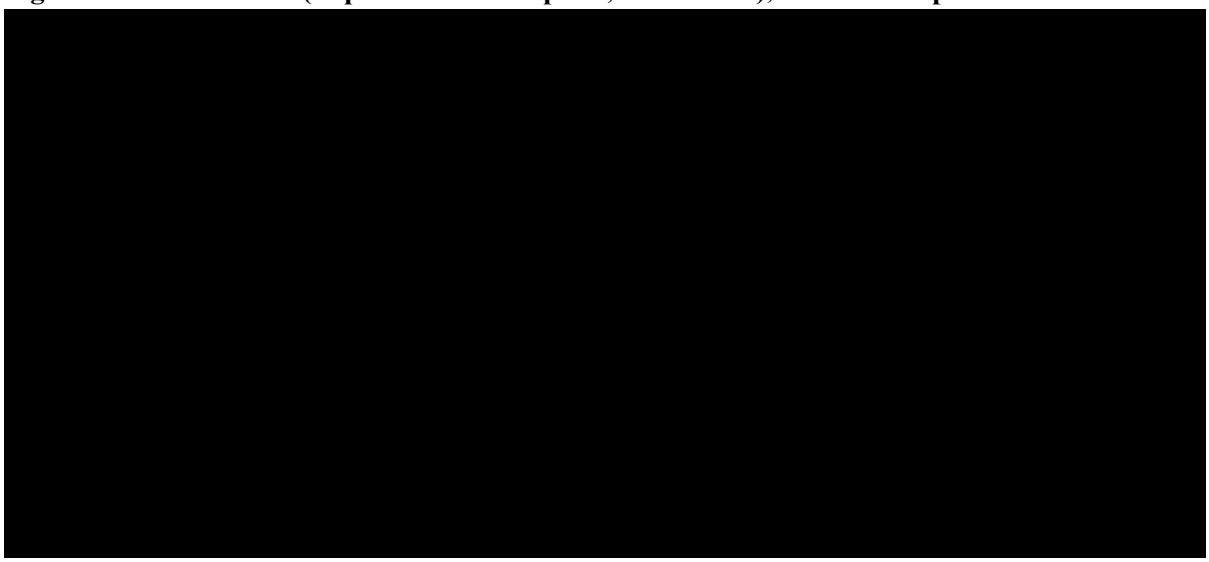
Figure 5.2: PSA CE-plane (selpercatinib PAS price, discounted), *RET* fusion-positive TC

Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; CE = cost effectiveness; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 5.3: PSA CEAC (selpercatinib PAS price, discounted), *RET*-mutant MTC

Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; CEAC = cost effectiveness acceptability curve; MTC = medullary thyroid cancer; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection

Figure 5.4: PSA CEAC (selpercatinib PAS price, discounted), *RET* fusion-positive TC



Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; CEAC = cost effectiveness acceptability curve; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer

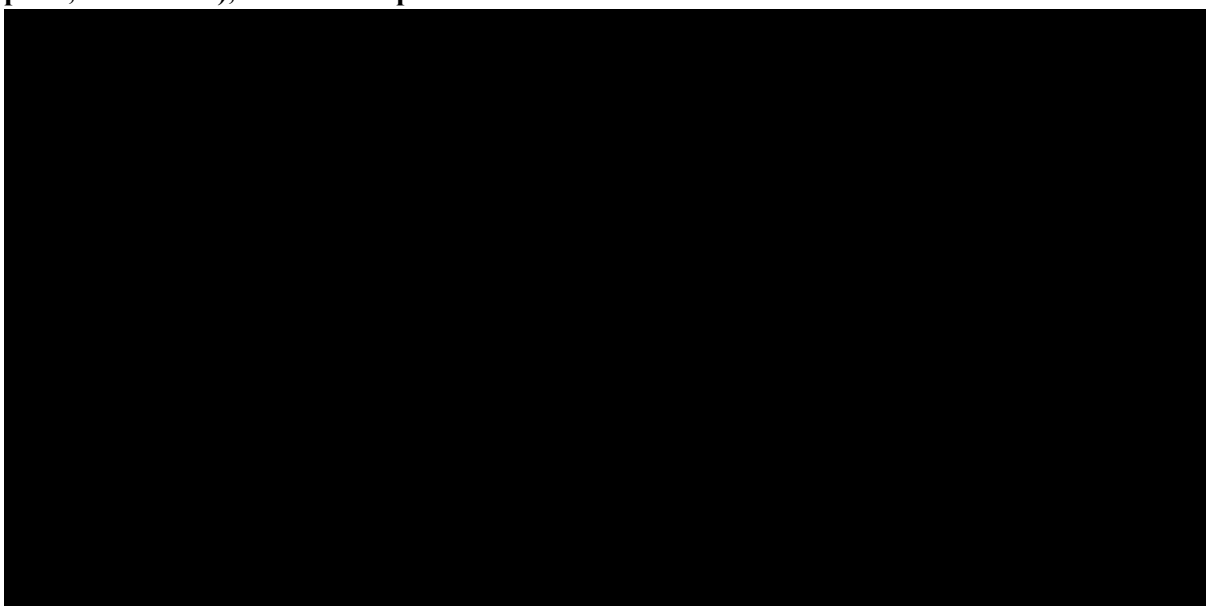
5.2.2 Deterministic sensitivity analysis (DSA)

The company also conducted deterministic sensitivity analyses (DSAs) where all input parameters, for which there were only a point estimate value in the model (these can be found in the "Variables - MTC" and "Variables - TC" sheets sheet), were varied by ±10% of their mean value. Figure 5.5 and Figure 5.6 present the tornado diagrams for selpercatinib versus BSC, showing the 25 parameters with the largest influence on the ICERs for the *RET*-mutant MTC and the *RET* fusion-positive TC populations, respectively. For both populations, the discount rate for health outcomes and costs, the utility value used in progression-free health state utility as well as the costs in the progression-free health state were the most influential parameters.

Figure 5.5: DSA tornado diagram for ICER of selpercatinib versus BSC (selpercatinib PAS price, discounted), *RET*-mutant MTC

Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; DSA = deterministic sensitivity analysis; ECG = electrocardiogram; ICER: incremental cost-effectiveness ratio; MTC = medullary thyroid cancer; PAS = Patient Access Scheme; QALY = quality-adjusted life year; *RET* = rearranged during transfection

Figure 5.6: DSA tornado diagram for ICER of selpercatinib versus BSC (selpercatinib PAS price, discounted), RET fusion-positive TC



Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; DSA = deterministic sensitivity analysis; ECG = electrocardiogram; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer

5.2.3 Scenario analyses

The company presented four scenario analyses for the *RET*-mutant MTC population and three scenario analyses for the *RET* fusion-positive TC population to assess the robustness of the model results to changes in some modelling assumptions. A summary of the results of these scenarios is provided in Table 5.7.

Table 5.7: Summary of company scenario analyses for the *RET*-mutant MTC and *RET* fusion-positive TC populations (selpercatinib PAS price, discounted)

Scenario	Description (base-case)	Description (scenario)	Inc. Costs (£)	Inc. QALYs (Weighted QALY 1.2)	ICER (£/QALY) (ICER with weighted QALY 1.2)
***RET*-mutant MTC**					
Base-case	-	-	[redacted]	[redacted]	48,078 (40,065)
PFS extrapolation (both treatment arms)	Loglogistic	Gamma	[redacted]	[redacted]	44,570 (37,141)
		Spline knot 1	[redacted]	[redacted]	49,130 (41,942)
OS extrapolation (both treatment arms)	Stratified Weibull (2.0 adjustment factor applied to selpercatinib)	Stratified gamma (2.0 adjustment factor applied to selpercatinib)	[redacted]	[redacted]	47,320 (39,433)
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted]	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	46,911 (39,093)
***RET* fusion-positive TC**					
Base-case	-	-	[redacted]	[redacted]	43,567 (36,306)
PFS extrapolation (both treatment arms)	Stratified Weibull	Exponential	[redacted]	[redacted]	46,224 (38,520)
OS extrapolation (both treatment arms)	Piecewise exponential (1.2 adjustment factor applied to selpercatinib)	Weibull (1.2 adjustment factor applied to selpercatinib)	[redacted]	[redacted]	41,147 (34,289)
TTD approach	Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted]	Selpercatinib TTD is assumed equal to PFS	[redacted]	[redacted]	41,813 (34,844)

Scenarios are based on Table 93 in the CS.[5]

BSC = best supportive care; CS = company submission; ICER = incremental cost-effectiveness ratio; MTC = medullary thyroid cancer; OS = overall survival; PFS = progression-free survival; PAS = Patient Access Scheme; QALYs = quality-adjusted life years; *RET* = rearranged during transfection; TC = thyroid cancer; TTD = time to discontinuation

5.3 Model validation and face validity check

The company reported that, as the model is largely consistent with the model used in 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 the ongoing selpercatinib appraisal in untreated advanced thyroid cancer with *RET* alterations (ID6132).[4, 36]

Verification of input data and validation of programming were performed by an independent reviewer and an independent health economist.

As no previous economic evaluations have been performed in *RET*-altered TC for patients who have previously received systemic treatment, cross validation was not possible.

As part of TA742 and NICE ID6132, input from clinical experts 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.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Explanation of the EAG adjustments

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case includes few changes to the original cost effectiveness model provided by the company base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and can be subdivided into three categories (derived from Kaltenthaler et al. 2016):[58]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong).
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

In the current assessment a few small errors were found by the EAG after clarification. The first error relates to the deterministic results reported by the company after the clarification for the *RET*-mutant MTC population. Here, accidently all costs, LYs and QALYs are reported using a 25-year time horizon instead of a 35-year time horizon (see Table 5.4 and Table 5.5, where al results were updated using a 35-year time horizon). Note that the impact is relatively small. The second error was noticed in Excel for the *RET*-mutant MTC population, as in the calculation of the age-adjusted utilities, the age and % of female from the *RET* fusion-positive TC population is used. The impact of this on the outcomes is minimal.

Errors that were found in the original model during clarification were corrected by the company in a revised electronic model. In addition, no violations were identified.

The EAG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- The company base-case assumed a log-logistic parametric model for the PFS of the *RET*-mutant MTC population, arguing that it aligns with clinical expectations and the Committee preferences in TA742.[4] Considering 1) that in the current appraisal longer follow-up data from the LIBRETTO-001 trial are used as compared to the data used in TA742, 2) the visual fit and AIC/BIC statistics indicating that the gamma distribution would provide a better fit to the observed data as compared to the loglogistic model, and 3) the fact that the gamma distribution better matches with both the 10-year and 20-year PFS predictions provided by the clinical experts during the ongoing appraisal for selpercatinib in patients with untreated, advanced thyroid cancer with *RET* alterations (ID6132), the EAG prefers the gamma distribution to model PFS of the *RET*-mutant MTC population in the base-case analysis.
- The company base-case assumed a piecewise exponential parametric model for the OS of the *RET* fusion-positive TC population grounded on the premise this matched closer to the long-term OS ranges provided by the clinical experts and that it represented the Committee preferences in TA742.[4] However, in the clarification phase the EAG pointed out a reporting error for the piecewise model values. Following the company's correction, the piecewise exponential model was shown to be the 6th parametric model that matched closer to the OS ranges provided by the clinical experts (see Table 4.10). Also, the EAG considered that

selecting this option merely to coincide with the Committee's preferred option in TA742, disregards the longer follow-up data of the LIBRETTO-001 trial that is used in the current appraisal. Based on the clinical plausibility criterion, the stratified gamma or stratified Weibull would get close to the estimates provided by the clinical experts for selpercatinib and BSC, without the need to implement adjustment factors as in the company's approach. Also, in terms of AIC criteria these two model options are not different than the piecewise exponential. Therefore, the EAG selected the stratified gamma for the base-case analysis of the *RET* fusion-positive TC population.

The overview of the changes and the bookmarks for the justification of the EAG changes are presented in Table 6.1.

Table 6.1: Company and EAG base-case preferred assumptions

Base-case preferred assumptions	Company	EAG	Justification for change
***RET*-mutant MTC population**			
PFS model	loglogistic	gamma	See section 4.2.6.2
***RET* fusion-positive TC population**			
OS model	piecewise exponential	stratified gamma	See section 4.2.6.4

EAG = Evidence Assessment Group; MTC = medullary thyroid cancer; OS = overall survival; PFS = progression free survival; QALYs = quality-adjusted life years; *RET* = rearranged during transfection; TC = thyroid cancer.

6.1.2 Additional scenarios conducted by the EAG

After the proposed changes were implemented in the company's model, the EAG performed the following exploratory scenario analyses to investigate the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Scenario set 1: Alternative models for OS (Sections 4.2.6.2 and 4.2.6.4)

The EAG explored the impact of using alternative models to fit the OS data from the LIBRETTO-001 trial for both populations. Specifically, for the OS of the *RET*-mutant MTC population, the EAG considered the loglogistic and the stratified gamma parametric functions, combined with an adjustment factor of 2.5 at 5 years for the selpercatinib arm. Furthermore, the EAG has aligned with the EAG's approach during the appraisal for selpercatinib in untreated patients (ID6132)[35] and has run additional scenarios in which the adjustment factor was varied based on the company's preferred parametric model. These were an optimistic and a pessimistic scenario that aligned with the stratified Weibull model, but with a lower adjustment factor of 1.5 at 5 years (optimistic scenario) and a higher adjustment factor of 3.5 at 5 years (pessimistic scenario), to reach to the limits of the clinical experts' plausible ranges.

For the OS of the *RET* fusion-positive TC population, the EAG considered the stratified Weibull (without adjustment factor) as an alternative parametric function. Furthermore, the EAG has aligned with the EAG's approach during the appraisal for selpercatinib in untreated patients (ID6132)[35] and has run additional scenarios in which the adjustment factor was varied based on the company's preferred parametric model. These were an optimistic and a pessimistic scenario that aligned with the piecewise exponential model, but with a lower adjustment factor adjustment factor of 0.9 at 5

years (optimistic scenario) and a higher adjustment factor of adjustment factor of 1.5 at 18 months (pessimistic scenario), to reach to the limits of the clinical experts' plausible ranges.

6.1.2.2 Scenario set 2: Alternative models for PFS (Sections 4.2.6.2 and 4.2.6.4)

The EAG also explored the impact of using alternative models to fit the PFS data from the LIBRETTO-001 trial. For the *RET*-mutant MTC population, the EAG considered the Weibull function as per company's scenario analysis. For the *RET* fusion-positive TC population, the EAG explored the impact of using the exponential extrapolation as per company's scenario analysis.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 EAG base-case results

In Section 6.1 the EAG base-case was defined, which was based on various changes compared to the company base-case following the clarification phase. Table 6.2 shows the deterministic CE results of the EAG preferred base-case analysis. All results are discounted. As with the company base-case, this analysis includes a PAS, accounting for a simple discount of [redacted] for selpercatinib. Table 6.2 presents unweighted QALYs while the QALYs and ICERs in brackets are based on a QALY weight equal to 1.2.

For the *RET*-mutant MTC patient population, the EAG's preferred curve for PFS extrapolation led to an ICER of £44,476 per QALY gained. The ICER for this population was lower than the company base-case ICER of £48,078 per QALY gained (see Table 5.5), due to the lower number of patients in the PF health state estimated by the gamma distribution (EAG's preferred option) as compared to the loglogistic (company's preferred option). The increase in the number of PD patients led to less treatment costs, while the decrease in QALYs gained was also small due to the fact patients would spend more time in PD which is related to a lower utility value.

For the *RET* fusion-positive TC patient population, the EAG's preferred curve for OS extrapolation increased the ICER to £46,699 per QALY gained as compared to the company's base-case ICER of £43,567 per QALY gained (see Table 5.5). This increase is primarily attributed to the decrease in QALYs, resulting from the slightly more pessimistic survival curve (stratified gamma) in the EAG approach as compared to the company's preferred approach (piecewise exponential). The total estimated costs remained approximately similar across these two options.

Table 6.2: EAG preferred base-case deterministic cost effectiveness results (selpercatinib PAS price, discounted)

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
***RET*-mutant MTC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,476 (37,063)
BSC	16,562	2.67	1.90	-			
***RET* fusion-positive TC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,699 (38,916)
BSC	15,452	2.06	1.47				

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
Based on the electronic model following the clarification phase.[1, 2] *Values in the parenthesis account for a QALY weight of 1.2 in both populations. BSC = best supportive care; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; PAS = patient access scheme; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer.							

Table 6.3 shows the probabilistic cost effectiveness results of the EAG preferred base-case analysis. All results are discounted. The probabilistic results are aligned with the deterministic EAG base-case results. The cost effectiveness planes in Figure 6.1 and Figure 6.2 show that all simulations fell in the North-East quadrant for both patient populations. It is also clear that the results for the *RET* fusion-positive TC patient population are associated with more uncertainty than those for the *RET*-mutant MTC patients, likely due to the 5-fold larger sample size available for the analysis of OS and PFS in the *RET*-mutant MTC population compared to the *RET* fusion-positive TC population.

The CEAC in Figure 6.3 shows that the probability that selpercatinib versus BSC is cost effective for the *RET*-mutant MTC population at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] respectively, when using the EAG preferred base-case assumptions. When a severity weight of 1.2 is applied, these percentages become [redacted] and [redacted], respectively.

For the *RET* fusion-positive TC population, the CEAC in Figure 6.4 shows that the probability that selpercatinib versus BSC is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted]. When a severity weight of 1.2 is applied, these percentages become [redacted] and [redacted], respectively.

Table 6.3: EAG preferred base-case probabilistic cost effectiveness results (selpercatinib PAS price, discounted)

Population/ Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
***RET*-mutant MTC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,454 (37,045)
BSC	16596	2.68	1.91				
***RET* fusion-positive TC**							
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,505 (38,754)
BSC	15,537	2.01	1.47				
Based on the electronic model following the clarification phase.[1, 2] *Values in the parenthesis account for a QALY weight of 1.2 in both populations. BSC = best supportive care; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; PAS = patient access scheme; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer							

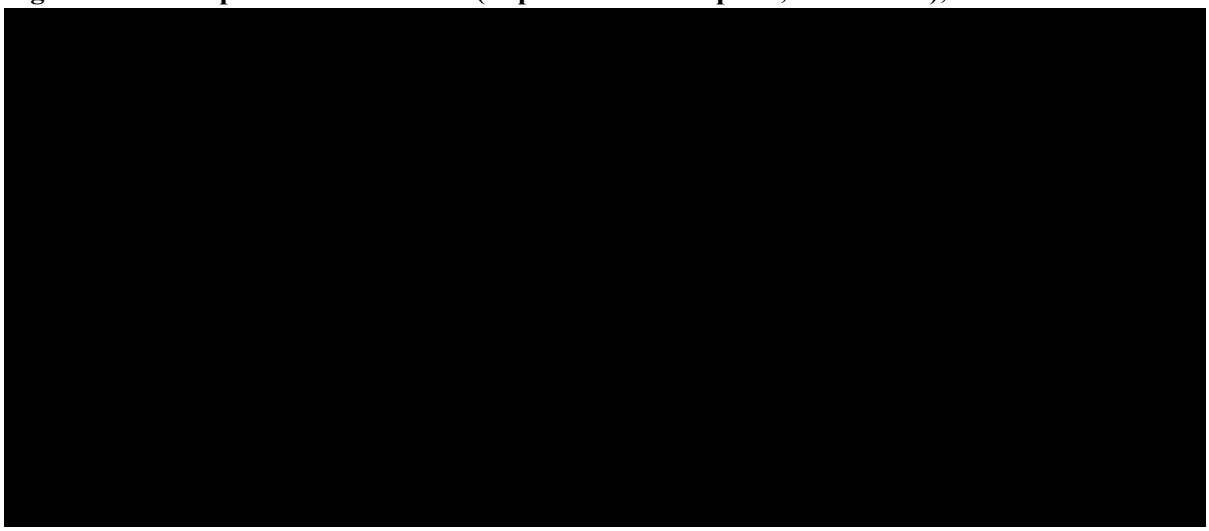
Figure 6.1: EAG probabilistic CE-plane (selpercatinib PAS price, discounted), *RET*-mutant MTC

Based on electronic model submitted following the clarification phase[2]
BSC = best supportive care; CE = cost-effectiveness; EAG = external assessment group; MTC = medullary thyroid cancer; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection

Figure 6.2: EAG probabilistic CE-plane (selpercatinib PAS price, discounted), *RET* fusion-positive TC

Based on electronic model submitted following the clarification phase[2]
BSC = best supportive care; CE = cost-effectiveness; EAG = external assessment group; PAS = patient access scheme; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer

Figure 6.3: EAG probabilistic CEAC (selpercatinib PAS price, discounted), RET-mutant MTC



Based on electronic model submitted following the clarification phase[2]
BSC = best supportive care; CEAC = cost-effectiveness acceptability curve; EAG = external assessment group; MTC = medullary thyroid cancer; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; *RET* = rearranged during transfection

Figure 6.4: EAG probabilistic CEAC (selpercatinib PAS price, discounted), *RET* fusion-positive TC

Based on electronic model submitted following the clarification phase.[2]
BSC = best supportive care; CEAC = cost-effectiveness acceptability curve; EAG = external assessment group; PAS = patient access scheme; QALY = quality-adjusted life year; *RET* = rearranged during transfection; TC = thyroid cancer

6.2.2 Impact individual adjustments by EAG to company base-case

Tables 6.4 and 6.5 show the individual adjustments that were made by the EAG for the two subpopulations, resulting in the new EAG base-case, and how the EAG base-case compared to the company's original and updated (after clarification) CE results.

Table 6.4: Deterministic EAG base-case versus company base-case (selpercatinib PAS price, discounted), *RET*-mutant MTC

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
CS original base-case					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	47,681
BSC	17,085	1.51	-		
CS base-case following the clarification phase					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	48,078 (40,065)
BSC	16,562	1.91			
EAG base-case: individual impact of using gamma distribution to model PFS					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	44,476 (37,063)
BSC	16,562	1.90	-		

Based on the electronic model following the clarification phase[1, 2]
*Values in the parenthesis account for a QALY weight of 1.2 in both populations.
BSC = best supportive care; CS = company submission; EAG = external assessment group; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; PAS = patient access scheme; PFS = progression-free survival; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer

Table 6.5: Deterministic EAG base-case versus company (selpercatinib PAS price, discounted), *RET* fusion-positive TC

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
CS original base-case					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	45,047
BSC	16,030	1.27	-		
CS base-case following the clarification phase					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	43,567 (36,306)
BSC	15,898	1.65	-		
EAG base-case: individual impact of using the stratified gamma distribution to model OS					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	46,699 (38,916)
BSC	15,452	1.47			

Based on the electronic model following the clarification phase[1, 2]
*Values in the parenthesis account for a QALY weight of 1.2 in both populations.
BSC = best supportive care; CS = company submission; EAG = external assessment group; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; OS = overall survival; PAS = patient access scheme; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer

6.3 Exploratory scenario analyses conducted by the EAG

The exploratory scenario analyses of the EAG are presented in Table 6.6 and Table 6.7. In all scenarios presented by the EAG the ICER remained above the commonly used thresholds of £20,000 and £30,000 per QALY gained.

For the *RET*-mutant MTC population, the scenario that led to the largest ICER increase was the pessimistic scenario suggested by the EAG during the appraisal for selpercatinib in untreated patients (ID6132),[35] increasing the ICER to £57,185 per QALY gained. The scenarios where OS was modelled using the loglogistic or stratified gamma function, combined with an adjustment factor of 2.5 at 5 years for selpercatinib led to modest increases in the ICER, at £48,516 and £48,148 per QALY gained, respectively. Only the optimistic scenario suggested by the EAG for the appraisal for selpercatinib in untreated patients (ID6132),[35] i.e. using the stratified Weibull to model OS, combined with an adjustment factor of 1.5 at 5 years for selpercatinib, decreased the ICER to £39,370 per QALY gained.

For the *RET* fusion-positive TC population, using a piecewise exponential model to model OS (combined with an adjustment factor of 1.5 at 18 months for selpercatinib) led to the largest ICER increase to £54,333. A modest increase in ICER, to £49,541 per QALY gained, is seen when the PFS is modelled using a Weibull function. Only the optimistic scenario, as suggested by the EAG for ID6132,[35] i.e. using a piecewise OS exponential model combined with an adjustment factor adjustment factor of 0.9 at 5 years decreased the ICER, to £38,836 per QALY gained.

Table 6.6: EAG scenario analyses (conditional on EAG base-case) (selpercatinib PAS price, discounted), *RET*-mutant MTC

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
EAG base-case (PFS gamma, OS stratified Weibull 2.0)					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	44,476 (37,063)
BSC	16,562	1.90			
OS loglogistic, combined with an adjustment factor of 2.5 at 5 years for selpercatinib					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	48,516 (40,430)
BSC	17621	2.31			
OS stratified gamma, combined with an adjustment factor of 2.5 at 5 years for selpercatinib					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	48,148 (40,123)
BSC	16499	1.88			
OS stratified Weibull, combined with an adjustment factor of 1.5 at 5 years for selpercatinib (optimistic scenario)					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	39,370 (32,808)
BSC	16,562	1.90			
OS stratified Weibull, combined with an adjustment factor of 3.5 at 5 years for selpercatinib (pessimistic scenario)					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	57,185 (47,654)
BSC	16,562	1.90			
PFS Weibull					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	42,489 (35,408)
BSC	16.562	1.90			

Based on the electronic model following the clarification phase.[1, 2]
*Values in the parenthesis account for a QALY weight of 1.2 in both populations.
BSC = best supportive care; EAG = external assessment group; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; OS = overall survival; PAS = patient access

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
scheme; PFS = progression-free survival; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer;					

Table 6.7: EAG scenario analyses (conditional on EAG base-case) (selpercatinib PAS price, discounted), *RET* fusion-positive TC

Population/ Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs*	ICER (£/QALY)*
EAG base-case (PFS stratified Weibull, OS stratified gamma)					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	46,699 (38,916)
BSC	15,452	1.47			
OS stratified Weibull					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	46,844 (39,037)
BSC	15,468	1.48			
OS piecewise exponential model, combined with an adjustment factor adjustment factor of 0.9 at 5 years (optimistic scenario)					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	38,836 (32,363)
BSC	15,898	1.65			
OS piecewise exponential model, combined with an adjustment factor of 1.5 at 18 months (pessimistic scenario)					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	54,333 (45,278)
BSC	15,898	1.65			
PFS exponential model					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	49,541 (41,285)
BSC	15,452	1.47			
Based on the electronic model following the clarification phase.[1, 2] *Values in the parenthesis account for a QALY weight of 1.2 in both populations. BSC = best supportive care; EAG = external assessment group; ICER = incremental cost effectiveness ratio; MTC = medullary thyroid cancer; LYG = life years gained; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; *RET* = rearranged during transfection; QALYs = quality-adjusted life years; TC = thyroid cancer;					

6.4 Conclusions of the cost effectiveness section

The main issue in the cost effectiveness analyses are the uncertainties in the estimates of both the relative treatment effectiveness as the PFS and OS per treatment arm for both populations, as this has a direct and potentially large impact on the ICERs. These issues have not been resolved compared to the original appraisal TA742,[4] despite the longer follow-up data available from the LIBRETT0-001 trial.

For the population of patients with RET-mutant MTC comparative effectiveness was estimated through a MAIC. As also discussed in section 4, this analysis was affected by several major limitations:

1. The company used survival data for a mixed population (consisting of naïve and previously treated patients) for both selpercatinib and BSC arms which is inconsistent with the population that is relevant for the decision problem of this appraisal, i.e. only previously treated patients.

As a result, any ICER that follows from this comparison is unlikely to be an unbiased estimate of the true cost effectiveness.

2. Using the placebo arm from the EXAM trial to estimate OS for the BSC arm may not produce a valid estimation of OS with BSC, because in the placebo arm of the EXAM trial, 49.5% of patients received a subsequent systemic therapy,[9] which does generally not happen in NHS clinical practice.
3. Also, uncertainty remains due to potential unobserved or unadjusted for confounding variables. When confounding variables were adjusted for, in absence of baseline characteristics for the placebo arm in EXAM a compromise was made to match patients using data from the cabozantinib arm in EXAM instead of the placebo arm.

For the population of patients with *RET*-fusion positive TC comparative effectiveness was estimated through a naïve indirect comparison. This in itself is a major limitation, and other limitations can also be identified:

1. To inform the BSC arm in this population, the SELECT trial was selected.[10] A MAIC was considered not possible for this population, due to the lack of comparability between the trial population and the small patient numbers in LIBRETTO-001. However, this is a clear indication that naïve comparisons of selpercatinib versus placebo (from the SELECT trial) are likely to produce a biased estimate of the true cost effectiveness.
2. As for the RET-mutant MTC population, again LIBRETT0-001 trial data from both the systemic therapy naïve and non-naïve patients were pooled, in order to align with the available data from the SELECT trial for BSC. This is contrary to the population defined for the decision problem of this appraisal, i.e. only previously treated patients. As mentioned earlier, this may well lead to a biased estimate of the true cost effectiveness.
3. The placebo patients in the SELECT trial were permitted to cross-over after progression, limiting the unbiased estimation of OS, despite the use of a rank preserving structural failure time model to adjust for the cross-over.
4. The SELECT trial was in patients with differentiated thyroid cancer (DTC) of whom the RET-fusion status was unknown, and it is unclear whether these patients are representative for RET-fusion positive TC patients.

To resolve part of the uncertainty around the use of the any-line MTC or TC patients versus pre-treated patients, the EAG asked the company to reproduce the survival analyses by removing the patients with RET-mutant MTC who were naïve to cabozantinib and/or vandetanib and patients with RET fusion-positive TC that were naïve to prior lenvatinib and/or sorafenib and include these results in the scenario analyses. However, the company declined to conduct such analyses arguing that this would be expected to substantially bias results against selpercatinib.

Other issues were also identified within the cost effectiveness analyses which are important to note, although secondary to the key issue of the extent to which the analyses conducted are able to reflect the relative efficacy in both populations.

The OS and PFS data were extrapolated using parametric survival curves. In both populations, due to the immature data, many curves provided a reasonable fit to the observed data, whilst showing large variation for the extrapolated part. In that regard, the EAG understands the company's prioritisation of clinical plausibility for the selection of the survival models over the goodness-of-fit measures and visual inspection. As part of the technology assessment for selpercatinib in untreated patients (ID6132),[35] ranges for 10 and 20-year PFS and OS were provided by clinical experts used to reflect clinical plausible values. Although all intermediate steps are reported in the CS, it was not always clear to the EAG how

the combination of information on goodness-of-fit (using AIC/BIC) and predicted (progression-free) survival at 10 and 20 years led to the final decision of a selected model to fit OS or PFS data. Especially, the decision to use the piecewise exponential model for the OS of the RET fusion-positive TC population remains uncertain. Whilst this model for OS provided an estimate of 10 years survival within the range predicted by clinical experts, the estimated 20-year survival was above the predicted range. Alternative options, the stratified Weibull and gamma model showed more pessimistic results, at 10 years below the predicted range and at 20 years within that range. It was not clear why the company would prefer the piecewise exponential model with an arbitrary adjustment factor to bring it closer to the predicted values, rather than using one of the most pessimistic options, i.e. the stratified Weibull or stratified gamma model. The EAG therefore, chose the stratified gamma for the EAG base-case analysis, while they also performed exploratory analyses using the stratified Weibull model and optimistic and pessimistic scenarios based on the piecewise exponential model as suggested by the EAG during the appraisal for selpercatinib in untreated patients (ID6132).[35]

In the model, time to treatment discontinuation in the selpercatinib arm, for both the RET-mutant MTC and RET fusion-positive TC populations, was set equal to PFS time plus the mean time from progression to treatment discontinuation, as observed in the previously treated RET-mutant MTC and the previously treated RET fusion-positive TC populations ([redacted] for MTC and [redacted] for TC). This approach aligned with the EAG's preferred approach in TA742 where fitting a curve based on trial TTD data yielded implausible TTD curves.[4] The EAG used the estimated time to treatment discontinuation models as incorporated in the electronic model to assess if one of these extrapolation options to the TTD data could improve estimations of time on treatment. Nonetheless, the EAG concluded that for the RET-mutant MTC population the same issue pertains as in the original appraisal: the alternative TTD extrapolation options led to clinically implausible outcomes. For the RET fusion-positive TC population, as in TA742,[4] the Weibull and gamma distributions would be deemed plausible for the TTD data, but the differences with the company's approach would be small. Therefore, the EAG considers the company's approach on the TTD analysis plausible.

Uncertainty exists regarding the HRQoL in the progression-free and progressed state:

1. The company did not update the 2019 SLR for health state utility values that was part of TA742.[4] The EAG found with a quick scan of the literature one more recently published mapping study that could potentially be useful.[24] Unfortunately, the company did not see this as an indication that an update of the SLR was needed and further did not respond on whether the study found by the EAG could be of use or not.
2. The EAG has some concerns about the use of the mapped utilities from the *RET* fusion-positive TC population for the model base-case. This relates to the extremely small sample size available in the *RET* fusion-positive TC any line group post-progression, i.e. [redacted]. In the *RET*-mutant MTC group on the other hand [redacted] were available, so not only more patients but also more assessments per patient. In that light, it seems relevant to explore possible explanations why these implausible (i.e. higher than before progression) post-progression utilities are observed. It might for example be related to continued treatment after progression in some patients, or with an uncommonly slow decline in HRQoL whilst already progressed.

Nevertheless, the EAG does agree with the use of the mapped utilities from the *RET* fusion-positive TC population, as they represent the more conservative set of utilities.

The company's deterministic base-case analysis for the RET-mutant MTC population (following the clarification phase) showed that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (incremental cost of [redacted]) than BSC amounting to an ICER of £48,078 per QALY

gained (without severity adjustment in QALYs). The company's deterministic base-case analysis for the RET fusion-positive TC population showed that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (incremental cost of [redacted]) than BSC amounting to an ICER of £43,567 per QALY gained (without severity adjustment in QALYs). All results are discounted and include a PAS for selpercatinib of [redacted].

The PSA of the company's model showed that the probability that selpercatinib versus BSC is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted]for both patient populations using the using the company base-case assumptions.

The EAG's preferences regarding the alternative extrapolation options for the model led to two changes to the company base-case analysis. First, for the RET-mutant MTC population, the EAG prefers the gamma distribution for PFS as compared to the loglogistic which was preferred by the company and aligned with the Committee's preferences in in TA742.[4] This change was grounded on 1) the longer follow-up data from the LIBRETTO-001 trial that is used in this appraisal as compared to the earlier data used in TA742, 2) the visual fit to the KM data reflected in the AIC/BIC statistics indicating that the gamma distribution would provide a better fit to the observed data as compared to the loglogistic model, and 3) the fact that the gamma distribution matches better with both the 10-year and 20-year PFS predictions provided by the clinical experts. Second, for the RET fusion-positive TC population, the EAG preferred to use the stratified gamma to model OS as compared to the piecewise exponential assumed by the company in their base-case. This decision is motivated by the fact 1) the stratified gamma would get closer to the estimates provided by the clinical experts for selpercatinib and BSC, without the need to implement adjustment factors for selpercatinib, and 2) in terms of AIC criteria this model option is not different than the piecewise exponential.

These changes in the model led to the following EAG preferred base-case incremental cost effectiveness results. For the RET-mutant MTC population, the total incremental costs for selpercatinib versus BSC reduced to [redacted] and the total incremental QALYs reduced to [redacted] leading to an ICER of £44,476 (£37,063 after severity weighting) per QALY gained. The probabilistic ICER of the EAG base-case amounts to £44,454 (£37,045 after severity weighting). The probability that selpercatinib versus BSC is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively, ([redacted] and [redacted] after severity weighting) for the RET-mutant MTC patient population using the EAG preferred base-case assumptions.

For the RET fusion-positive TC population, the total incremental costs for selpercatinib versus BSC reduced to [redacted] and the total incremental QALYs reduced to [redacted] leading to an ICER of £46,699 (£38,916 after severity weighting) per QALY gained. The probabilistic ICER of the EAG base-case amounts to £46,505 (£38,754 after severity weighting). The probability that selpercatinib versus BSC is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted], ([redacted] and [redacted] after severity weighting) for the RET fusion-positive TC patient population using the EAG preferred base-case assumptions.

Several scenarios were explored, and all led to ICERs that were above the thresholds of £20,000 and £30,000 per QALY gained. For the RET-mutant MTC population, the most substantial changes occurred when using the pessimistic and optimistic scenarios suggested by the EAG during the appraisal for selpercatinib in untreated patients (ID6132).[35] The first increased the ICER at £57,185 per QALY gained, while the second decreased the ICER to £39,370 per QALY gained. For the RET fusion-positive TC population, using an exponential function to model PFS and the optimistic scenario suggested by the EAG during the appraisal for selpercatinib in untreated patients (ID6132),[35] led to the largest ICER

changes. The first increased the ICER at £49,541 per QALY gained, whilst the second decreased the ICER to £38,836 per QALY gained.

It is important to realise that, given the problems with the estimation of relative treatment effectiveness of selpercatinib compared to BSC based on only a single-arm study, all ICERs mentioned above are potentially biased. This means that the overall uncertainty about the cost effectiveness is much larger than that indicated by all presented sensitivity and scenario analyses. Unfortunately, given the data currently available, these uncertainties cannot be resolved.

7. References

[1] National Institute for Health and Care Excellence. *Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]: Response to request for clarification from the EAG*, 2024 [accessed 28.5.24]

[2] Eli Lilly and Company. *Economic Model for Selpercatinib (LOXO-292) (ID6288 selpercatinib clarification response CEM 24052024CM [CON]) [Revised Excel file provided by the company after clarification]*, 2024 [accessed 27.5.24]

[3] National Institute for Health and Care Excellence. *Selpercatinib for treating advanced thyroid cancer with RET alterations (managed access review of TA742): Final scope*. London: NICE, 2024 [accessed 6.3.24]

[4] National Institute for Health and Care Excellence. *Selpercatinib for treating advanced thyroid cancer with RET alterations. NICE Technology appraisal guidance (TA742) [Internet]*. London: NICE, 2021 [accessed 25.4.23] Available from: www.nice.org.uk/guidance/ta742

[5] Eli Lilly and Company. *Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*, 2024 [accessed 16.4.24]

[6] Medicines Healthcare products Regulatory Agency (MHRA). *Summary of Products Characteristics. Retsevmo 40 mg hard capsule [As referenced in the CS]*, n.d. [accessed 12.5.23] Available from: https://mhraproducts4853.blob.core.windows.net/docs/860f80184d66809a5920fbe65478fff1d25f3542

[7] European Medicines Agency (EMA). *Retsevmo: EPAR Product Information [Internet]*, n.d. [accessed 12.6.24] Available from: https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_en.pdf

[8] NHS England. *National Cancer Drugs Fund (CDF) list (ver1.303) [Internet]*, 2024 [accessed 24.4.24] Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/

[9] Schlumberger M, Elisei R, Müller S, Schöffski P, Brose M, Shah M, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol 2017; 28(11):2813-9

[10] Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015; 372(7):621-30

[11] Eli Lilly and Company. *Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Appendices*, 2024 [accessed 16.4.24]

[12] Canadian Agency for Drugs and Technologies in Health. *PRESS - Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E) [Internet]*. Ottawa: CADTH, 2016 [accessed 16.11.20] Available from: https://www.cadth.ca/resources/finding-evidence/press

[13] Riemsma R, Wetzelaer P, Penton H, Chalker A, Ryczek E, Armstrong N, et al. *Selpercatinib for treating advanced thyroid cancer with RET alterations: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd, 2020 [accessed 11.6.24] Available from: https://www.nice.org.uk/guidance/ta742/evidence/committee-papers-pdf-9265004173

[14] Eli Lilly Company. Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off) [PDF provided by the company].

[15] National Institute for Health and Care Excellence. *Managed access agreement: selpercatinib for treating advanced thyroid cancer with RET alterations [TA742][Internet]*. London: NICE, 2021 [accessed 30.5.24] Available from: https://www.nice.org.uk/guidance/ta742/resources/managed-access-agreement-pdf-10883969965

[16] National Disease Registration Service (NDRS), NHS England. *Selpercatinib for treating advanced thyroid cancer with RET alterations – data review [Document provided by the company]*. Leeds: NDRS, n.d. [accessed 8.2.24]

[17] Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013; 31(29):3639

[18] Hu MI, Elisei R, Dedecjus M, Popovtzer A, Druce M, Kapiteijn E, et al. Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer. Endocr Relat Cancer 2019; 26(2):241-250

[19] Wells SA, Jr., Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012; 30(2):134-41

[20] Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014; 384(9940):319-28

[21] Latimer NR, Abrams KR. *NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching*. Sheffield: Decision Support Unit, ScHARR, 2014. 57p. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf

[22] Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE*. Sheffield: Decision Support Unit, ScHARR, 2015. 82p. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf

[23] National Institute for Health and Care Excellence. *Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]: Clarification questions*. London: NICE, 2024

[24] Huang D, Zeng D, Tang Y, Jiang L, Yang Q. Mapping the EORTC QLQ-C30 and QLQ H&N35 to the EQ-5D-5L and SF-6D for papillary thyroid carcinoma. Qual Life Res 2024; 33(2):491-505

[25] Houten R, Fleeman N, Kotas E, Boland A, Lambe T, Duarte R. A systematic review of health state utility values for thyroid cancer. Qual Life Res 2021; 30(3):675-702

[26] Fordham BA, Kerr C, de Freitas HM, Lloyd AJ, Johnston K, Pelletier CL, et al. Health state utility valuation in radioactive iodine-refractory differentiated thyroid cancer. Patient Prefer Adherence 2015; 9:1561

[27] National Institute for Health and Care Excellence. *Cabozantinib for treating medullary thyroid cancer. NICE Technology appraisal guidance (TA516) [Internet]* London: NICE, 2018 [accessed 25.4.23] Available from: www.nice.org.uk/guidance/ta516

[28] National Institute for Health and Care Excellence. *Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. NICE Technology appraisal guidance (TA535)[Internet]*. London: NICE, 2018 [accessed 25.4.23] Available from: www.nice.org.uk/guidance/ta535

[29] Wirth LJ, Subbiah V, Worden F, Solomon BJ, Robinson B, Hadoux J, et al. 2229P: Updated safety and efficacy of selpercatinib in patients with RET activated thyroid cancer: data from LIBRETTO-001. Presented at European Society for Medical Oncology 48th Congress (ESMO); 20-24 Oct 2023; Madrid, Spain [PDF provided by the company].

[30] Raez LE, Kang H, Ohe Y, Khanal M, Wang K, Han Y, et al. FPN 669P: Patient reported outcomes with selpercatinib in patients with RET driven cancers in the Phase 1/2 LIBRETTO-001 Trial. Presented at European Society for Medical Oncology 48th Congress (ESMO); 20-24 Oct 2023; Madrid, Spain [PDF provided by the company].

[31] National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual. NICE process and methods [PMG36] [Internet]*. London: National Institute for Health and Care Excellence, 2023 [accessed 10.1.24]. 200p. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

[32] Latimer N. *NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data.* Sheffield: Decision Support Unit, ScHARR, 2011. 52p. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf

[33] Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002; 21(15):2175-97

[34] Sherman SI, Clary DO, Elisei R, Schlumberger MJ, Cohen EEW, Schöffski P, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer 2016; 122(24):3856-64

[35] National Institute for Health and Care Excellence. *Selpercatinib for untreated advanced thyroid cancer with RET alterations [ID6132] [Internet]* London: NICE, 2024 [accessed 17.6.24] Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11047

[36] Eli Lilly and Company. *Selpercatinib for untreated advanced RET altered TC and MTC Clinical Expert Validation Interviews. Meeting Minutes 2023 [Data on file] [Document provided by the company*

[37] National Institute for Health and Care Excellence. *Cabozantinib for previously treated advanced differentiated thyroid cancer unsuitable for or refractory to radioactive iodine. NICE Technology appraisal guidance (TA928) [Internet]*. London: NICE, 2023 [accessed 16.1.24] Available from: www.nice.org.uk/guidance/ta928

[38] Khan I, Morris S, Pashayan N, Matata B, Bashir Z, Maguirre J. Comparing the mapping between EQ-5D-5L, EQ-5D-3L and the EORTC-QLQ-C30 in non-small cell lung cancer patients. Health Qual Life Outcomes 2016; 14:60

[39] Young TA, Mukuria C, Rowen D, Brazier JE, Longworth LCP. 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(7):912-26

[40] Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQ-C30 to the preference-based EQ-5D, SF-6D, and 15D instruments. Value Health 2009; 12(8):1151-7

[41] Marriott ER, van Hazel G, Gibbs P, Hatswell AJ. Mapping EORTC-QLQ-C30 to EQ-5D-3L in patients with colorectal cancer. J Med Econ 2017; 20(2):193-9

[42] National Institute for Health and Care Excellence. *Draft guidance consultation: Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy [Internet]*. London: NICE, 2024 [accessed 4.6.24] Available from: https://www.nice.org.uk/guidance/gid-ta11047/documents/draft-guidance

[43] Gou J, Cheng W, Lei J, Pan Q, You W, Cai M, et al. Health-related quality-of-life assessment in surgical patients with papillary thyroid carcinoma: a single-center analysis from Mainland China. Medicine 2017; 96(38)

[44] Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. Br J Cancer 2009; 101(3):387-9

[45] Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010; 13(5):509-18

[46] Hernández Alava M, Pudney S, Wailoo A. *NICE DSU Report: Estimating EQ-5D by age and sex for the UK [Internet]*. Sheffield: Decision Support Unit, ScHARR, 2022 [accessed 13.3.24]. 23p. Available from: https://www.sheffield.ac.uk/media/34059/download?attachment

[47] British National Formulary. *Selpercatinib: Medicinal Forms [Internet]*. London: BNF Publications, n.d. [accessed 12.6.24] Available from: https://bnf.nice.org.uk/drugs/selpercatinib-specialist-drug/#medicinal-forms

[48] Curtis L, Burns A. *Unit costs of health and social care: Personal Social Services Research Unit 2021 [Internet]*. Canterbury: University of Kent, 2022 [accessed 23.10.23] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/

[49] European Medicines Agency (EMA). *Retsevmo: Selpercatinib [Internet]*. Amsterdam: EMA, n.d. [accessed 19.6.23] Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo

[50] NHS England. *2021/22 National Cost Collection Data Publication [Internet]*. London: Department of Health, 2023 [accessed 17.6.24] Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/

[51] NHS England. *National genomic test directory [Internet]*, n.d. [accessed 26.4.23] Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/

[52] NHS England. *Accelerating genomic medicine in the NHS [Internet]*, n.d. [accessed 28.4.23] Available from: https://www.england.nhs.uk/long-read/accelerating-genomic-medicine-in-the-nhs/

[53] National Institute for Health and Care Excellence. *Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer. NICE Technology appraisal guidance (TA911) [Internet]*. London: NICE, 2023 [accessed 24.10.23] Available from: www.nice.org.uk/guidance/ta911

[54] Taccaliti A, Silvetti F, Palmonella G, Boscaro MCP. Genetic alterations in medullary thyroid cancer: diagnostic and prognostic markers. Curr Genomics 2011; 12(8):618-25

[55] Liu S, Gao A, Zhang B, Zhang Z, Zhao Y, Chen P, et al. Assessment of molecular testing in fine-needle aspiration biopsy samples: an experience in a Chinese population. Exp Mol Pathol 2014; 97(2):292-297

[56] Wells Jr SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the American Thyroid Association Guidelines Task Force on medullary thyroid carcinoma. Thyroid 2015; 25(6):567-610

[57] Versteegh MM, Ramos IC, Buyukkaramikli NC, Ansaripour A, Reckers-Droog VT, Brouwer WBF. Severity-adjusted probability of being cost effective. Pharmacoeconomics 2019; 37(9):1155-63

[58] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. Health Technol Assess 2016; 20(26):1-48

Appendix 1: Selpercatinib for treating advanced thyroid cancer with *RET* alterations (MA review of TA742) [ID6288] - Teams meeting between EAG and clinical expert

Date: 07/05/24

Present:

Nigel Armstrong (NA) – member of Evidence Assessment Group (EAG)

Marie Westwood (MW) – project lead, EAG

Maiwenn Al (MA) – lead health economist, EAG

Caroline Brammer (CB) – clinical expert, Consultant in Clinical Oncology, Clatterbridge Cancer Centre

The purpose of the meeting was for CB and the EAG to be introduced to each other and to elicit CB's expertise to aid construction of the EAG report.

The following questions were emailed to CB ahead of the meeting:

'To kick things off, we would very much welcome your assistance in establishing what is current UK clinical practice i.e., without selpercatinib. Note that the two populations of interest are:

- People with advanced *RET* fusion-positive TC who require systemic therapy after sorafenib or lenvatinib
- People with advanced *RET* mutation-positive MTC who require systemic therapy after cabozantinib or vandetanib

The comparator in the scope is simply described as best supportive care (BSC) or palliative care. Is this correct and perhaps you could provide an idea of what constitutes BSC.

We also wondered how frequently patients in each population would receive both kinds of systemic therapy i.e., one after the other e.g. sorafenib followed by lenvatinib.'

NA: asked CB what she considered to be SoC for the above two populations.

CB:

For *RET* fusion, use lenvatinib except if not tolerated, which is relatively rare and implied sorafenib

For *RET* mutation-positive MTC, use cabozantinib except if not tolerated, which is relatively rare and implied vandetanib

For both populations, there is no sequential systemic treatment (with the specified drugs) in the UK (sequential treatment does occur in US and Europe): the switch would be done within three months of commencement of first line treatment not on failure (which can mean many things). Therefore, on progression, use best supportive care (BSC), which includes analgesics, radiotherapy for any bone metastases and food supplements. Patients would be under the care of a palliative care consultant. CB

noted that if sorafenib or vandetanib were used because lenvatinib or cabozantinib not tolerated, the second option would usually be used within three months of failure.

MA: asked CB if there were any patient registries in the UK.

CB: No

CB: Pointed out that there was often a long delay in obtaining *RET* status because biopsies did not contain material suitable for testing ("failed for RNA analysis"), which meant that patient might have progressed before *RET* status was confirmed, thus ruling out treatment with selpercatinib. Therefore, there was a trend towards earier testing: it has recently become routine to request the tests when commencing first line therapy, but the pathway is slow and not fully established and still can lead to significant delays in results being available.

MW: asked CB if she knew of any trials that could provide comparator (BSC) data.

CB: Probably not.

NA: asked CB if she had any questions or wanted to make any other comments.

CB: resource consumption with this population is large relative to other cancers because patients have a longer survival.

Single Technology Appraisal

Selpercatinib for treating advanced thyroid cancer with RET alterations (MA review of TA742) [ID6288]

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 Friday 28 June** 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 Sources of comparator data for the indirect treatment comparisons (ITCs)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.3, Page 15, Section 1.4 of the EAG report states that: "However, because only an unanchored ITC (single arms only) was feasible, it is unclear why the company only seemed to consider RCTs as the source of comparator data." Page 102, Section 3.3.1 of the EAG report re-iterates this statement.	These statements should be removed.	It is inaccurate to state that the Company considered only randomised controlled trials (RCTs) as the source of comparator data; searches were conducted for all study designs in the rearranged during transfection (*RET*)-altered thyroid cancer (TC) and medullary thyroid cancer (MTC) populations, and RCTs only for the wider TC and MTC populations. Further clarification on this point may be found in the Company response to clarification question A.1.	Wording has been amended (Table 1.3 page 15 and Section 3.3.1, page 102) to clarify that different study design criteria were applied when considering studies in the *RET*-altered vs. wider TC and MTC populations.

Issue 2 Positioning of selpercatinib for patients with undifferentiated thyroid cancer

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, Section 2.1 of the EAG report states that: "The treatment pathway and proposed positioning of selpercatinib in patients with advanced *RET* fusion-positive TC, reported in the Company submission (CS) and illustrated in Figure 2.1.5 appears to indicate that selpercatinib is	Please amend this statement as follows: "The treatment pathway and proposed positioning of selpercatinib in patients with advanced *RET* fusion-positive TC, reported in the CS and illustrated in Figure 2.1,[5] appears to indicate that selpercatinib is currently available for patients with undifferentiated TC as an alternative to full thyroidectomy; **clarification from the company since submission indicates that**	Patients who are eligible for surgery (patients with resectable disease) would not receive selpercatinib in place of surgery. They would instead receive selpercatinib following surgery, if required. In order to provide clarification on this point, please see the updated treatment pathway diagram provided in	Most of the clarification noted by the company was already provided in the EAG comment (Section 2.1, page 26); additional text has been added to further clarify that, for patients with undifferentiated TC, selpercatinib would be received after surgery, if

currently available for patients with undifferentiated TC as an alternative to full thyroidectomy; it is the understanding of the Evidence Assessment Group (EAG) that TA742 recommended selpercatinib only after sorafenib or lenvatinib, which are given to patients with differentiated disease."	**for these patients, selpercatinib would be received after surgery, if required." I**t is the understanding of the Evidence Assessment Group (EAG) that TA742 recommended selpercatinib ~~**only**~~ after sorafenib or lenvatinib, which are given to patients with differentiated disease." **However, as per the National Cancer Drugs Fund list (last updated 24th June 2024), no prior treatment with a TKI is necessary for patients with undifferentiated TC in order to receive selpercatinib. Patients with *RET*-altered undifferentiated TC are therefore currently eligible to receive selpercatinib."[1]**	Appendix A. The EAG are correct in stating that TA742 recommended selpercatinib specifically for patients following sorafenib or lenvatinib. However, the Cancer Drugs Fund list confirms that patients with undifferentiated thyroid cancer are eligible for treatment with selpercatinib without prior treatment with kinase inhibitors, with clinical validation collected to support evaluation ID6132 supporting that patients with undifferentiated TC would not receive lenvatinib or sorafenib in clinical practice, and therefore would be eligible for selpercatinib.[1, 2] Patients with *RET* fusion-positive undifferentiated TC therefore form part of the population eligible for treatment with selpercatinib in UK clinical practice, and should be considered in this evaluation.	required.

Issue 3 Unique included studies in the clinical systematic literature review (SLR)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 35, Section 3.1.5 of the EAG report states that	Lilly thank the EAG for bringing this discrepancy to their attention and can	The N=18 datapoint is a factual inaccuracy and should be corrected. It may be useful	Text has been added to the EAG comment (Section 3.1.5, page 35) noting the

"The EAG notes that the number of unique included studies given in the PRISMA flow chart and accompanying text (n=24) does not match the number of studies reported in the 'Study characteristics for included studies' table (n=18). The EAG further notes that the report of the SLR, provided in Appendix D of the CS, does not include details of excluded studies."	confirm that this was a reporting error. The text should be amended as follows: "**A total of 24 unique studies were included in the clinical SLR**" In case useful for the EAG's reference, Table 1 in Appendix B provides a corrected, full list of included studies in the clinical SLR (May 2023 update). It should be noted that as per Table 18 in Appendix D.1.4, all missing trials from the complete reference list were considered in the feasibility assessment for the ITC in the *RET* fusion-positive TC population. As such, all included trials were considered in this feasibility assessment.	context to note that all included studies in the clinical SLR were considered as part of the feasibility assessment.	provision of this additional information.

Issue 4 Relevant comparators in UK clinical practice for the *RET*-altered TC and MTC populations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, Section 3.2.3.1 of the EAG report states that: "The EAG considers that the numbers of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC patient population who had received other types of systemic therapy, including apparent sequential use of both cabozantinib and vandetanib, raises the question of whether all	Please consider revising this sentence to acknowledge that the sequential use of kinase inhibitors, and other systemic therapies (other than those specified in TA742 and radioactive iodine, in TC), for the treatment of *RET*-altered TC and MTC are not permitted in UK clinical practice.[1, 2] As such, the relevant comparator to selpercatinib for adults and adolescents aged 12 years and older with advanced *RET*-mutant MTC who require systemic	The LIBRETTO-001 trial is a multinational trial conducted across 16 countries, thus allowing sufficient numbers of patients with *RET*-altered cancers to be recruited into the study. As such, it should be acknowledged that the distribution of prior treatments received by patients with *RET*-mutant MTC and *RET* fusion-positive TC prior to enrolment	The quoted EAG statements have been removed from the EAG report.

relevant comparators (as used in UK clinical practice) have been considered for this population." Page 54, Section 3.2.3.2 of the EAG report states that: "The EAG considers that the numbers of patients in the prior systemic therapy *RET* fusion-positive TC patient population who had received systemic therapies other than lenvatinib or sorafenib, including apparent sequential use of both lenvatinib and sorafenib, raises the question of whether all relevant comparators (as used in UK clinical practice) have been considered for this population."	therapy following cabozantinib or vandetanib, and adults and adolescents aged 12 years and older with advanced *RET* fusion-positive TC who require systemic therapy following lenvatinib or sorafenib, is best supportive care (BSC) only as no other treatments are funded in UK following progression on these kinase inhibitors.	reflects the multinational design of the trial, in which each country has its own distinct, approved treatment regimen. Relevant comparators for patients with *RET* fusion-positive TC in this evaluation were selected based on available NICE guidance (TA742) and the corresponding National Cancer Drugs Fund list, which states that patients with *RET* fusion-positive TC are eligible for treatment with lenvatinib and sorafenib in the first-line setting, and, following progression, sequential use of TKIs (lenvatinib and sorafenib) are not funded in the UK.[1, 2] Relevant comparators for patients with *RET*-mutant MTC in this evaluation were also selected based on TA742 and the National Cancer Drugs Fund list, which states that patients with *RET*-mutant MTC are eligible for treatment with cabozantinib and vandetanib in the first-line setting, and, following progression, sequential use of TKIs (cabozantinib and vandetanib) are not funded in the UK.[1, 2] As such, the comparator used in this evaluation (BSC, in both populations) reflects clinical	

		practice in the UK. It should also be noted that only BSC is considered as a comparator in the *RET*-mutant MTC and *RET* fusion-positive TC populations the NICE final scope.	

Issue 5 Prior treatments received by patients in the *RET* fusion-positive TC population (1/2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54, Section 3.2.3.2 of the EAG report states that: "The EAG notes an inconsistency in the data presented for the numbers of patients in the prior systemic therapy *RET*-fusion positive TC population who had previously received lenvatinib, sorafenib, or both; if, as indicated N=26 had received lenvatinib, N=9 had received sorafenib and N=4 had received both, then the total number of patients who received a prior treatment regimen specified in the original NICE guidance for selpercatinib in this indication (TA742) would be [redacted] not [redacted]."	This statement should be removed.	As per the Company response to clarification question A.12 part c), the total number of patients with *RET*-fusion positive TC who received a prior treatment regimen specified in the original NICE guidance for selpercatinib in this indication (TA742) includes patients who had previously been treated with either lenvatinib **or** sorafenib, [redacted], or with both lenvatinib **and** sorafenib, N=4. As such, in the LIBRETTO-001 trial (13th January 2023 data cut-off [DCO]), the total number of patients who received a prior treatment regimen specified in the original NICE guidance for selpercatinib in this indication (TA742) would be [redacted] not [redacted].	The quoted text (Section 3.2.3.2, page 55) has been amended for clarity; TA742 does not recommend the sequential use of lenvatinib **and** sorafenib, and (as noted in the company's earlier comments) sequential use is not current UK clinical practice.

Issue 6 Prior treatments received by patients in the *RET* fusion-positive TC population (2/2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 88, Section 3.2.6.2 of the EAG report states that: "Clinical expert opinion (sought by the EAG, Appendix 1) has indicated that the UK treatment pathway for the *RET* fusion-positive TC population is lenvatinib (with sorafenib generally only used where lenvatinib is not tolerated), followed by selpercatinib or BSC; i.e., lenvatinib and sorafenib are not routinely used sequentially in UK clinical practice. The EAG notes that prior treatment with both ≥2 systemic therapies occurred in [redacted] of prior systemic therapy *RET* fusion-positive TC population in the LIBRETTO-001 study and appeared to be associated with a [redacted] ORRs than one prior systemic therapy."	Please amend this text as follows: "Clinical expert opinion (sought by the EAG, Appendix 1) has indicated that the UK treatment pathway for the *RET* fusion-positive TC population is lenvatinib (with sorafenib generally only used where lenvatinib is not tolerated), followed by selpercatinib or BSC; i.e., lenvatinib and sorafenib are not routinely used sequentially in UK clinical practice. The EAG notes that **small number of patients in the** prior systemic therapy *RET* fusion-positive TC population in the LIBRETTO-001 study **had previously been treated with both lenvatinib and sorafenib (4 [9.8%]), which is reflective of UK clinical practice.**"	This section of the EAG report currently implies that [redacted] patients had received prior treatment with ≥2 kinase inhibitors, which is factually inaccurate. Instead, this number represents the number of patients who received ≥2 systemic therapies including radioactive iodine therapy, as per Page 91, Section 4.5.1.3 of the LIBRETTO-001 clinical study report (CSR). Radioactive iodine therapy can be considered routine treatment for patients with TC in the UK.[1, 3] As detailed in Issue 5 above, in the prior systemic therapy *RET* fusion-positive TC population, [redacted] patients had previously been treated with lenvatinib **or** sorafenib, while 4 patients had previously been treated with both lenvatinib **and** sorafenib. Therefore, presenting the number of patients in the of prior systemic therapy *RET* fusion-positive TC population who had prior treatment with ≥2 systemic therapies, which included both kinase inhibitors and radioactive iodine therapy, could be	The quoted EAG comment has been amended, in line with the company's suggestion.

		misleading and should be removed.	

Issue 7 Piecewise exponential extrapolation for the *RET* fusion-positive TC population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135, Section 4.2.6.4 of the EAG report states that: "Specifically, the company used 19 parametric models to inform the OS and PFS of the *RET*-mutant MTC population and the PFS of the *RET*-fusion positive TC population, whilst they also fitted a piecewise exponential model for the OS of the *RET* fusion-positive TC population (20 in total)."	Please amend this statement as follows: "Specifically, the company used 19 parametric models to inform the OS and PFS of the *RET*-mutant MTC population and the PFS of the *RET*-fusion positive TC population, whilst they also fitted a piecewise exponential model for the OS of the *RET* fusion-positive TC population (20 in total). **The piecewise exponential extrapolation was explored in this evaluation in recognition of the approach used in prior evaluation TA535; this extrapolation was explored in TA742 for the same reason."**[4]	The rationale behind exploring this survival extrapolation should be added, for context.	This is not a factual error. The EAG is happy to provide the context as provided here by the company, but wants to emphasise that this context was not given by the company in their submission. We have added the text in the paragraph above Table 4.9: *Note that compared to the RET mutant MTC population here the piecewise exponential extrapolation was also explored, according to the company in recognition of the approach used in prior evaluation TA535. This extrapolation was explored in TA742 for the same reason.* In addition, the EAG comment c) on page 136 was removed.

Issue 8 Best fit of the stratified models versus independent models of survival data extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 125, Section 4.2.6.2 of the EAG report states that: "Although the company presents a variety of models including joint models (assuming PH) and stratified models, it is currently unclear to the EAG if estimation of independent models as per the NICE DSU TSD 14 guidance on survival data extrapolations would provide a better fit."	Please amend the statement as follows, to remove the latter half of the sentence, leaving only the following statement: "The company presents a variety of models including joint models (assuming PH) and stratified models"	Lilly understands the concern regarding the stratified and independent model. However, the independent model and stratified model should be similar. For example, Lilly has considered a Weibull distribution and fit these two models in R using flexsurvreg package (code provided in Appendix C: below, where the stratified model is model1 and independent model is model3). The estimated shape and scale parameters are extremely similar in the two models, as shown in the results in Table 2 in Appendix C: below. While AIC/BIC statistics cannot be directly compared between the two models, the extremely similar parameters do not provide any rationale to suggest that the use of independent models would provide a better fit to the observed data from LIBRETTO-001.	The EAG agrees with the company that it makes sense that the independent and stratified model should be similar, and we are happy that the company has included an example to show this. What the EAG was less sure off when we wrote our comment is whether the SEs for the coefficients would also be similar, or if the stratified model specification somehow leads to 'borrowing strength' between the 2 treatment arms. The EAG was furthermore somewhat confused by the company's response to the clarification letter, where the company stated: *This can be seen throughout the Company submission, where the results of both independently fitted and stratified models have been presented throughout Section B.3.3, and the*

			selection of the most appropriate extrapolation in each case considered both stratified and independently fitted models. This statement appeared at odds with the CEM where stratified and non-stratified models were explored. But the EAG is happy to remove the second part of the sentence, as suggested by the company.

Issue 9 Removal of the stratified spline knot 1, 2 and 3 models from the cost-effectiveness model (CEM) for survival estimates in the RET fusion-positive TC population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135, Section 4.2.6.4 of the EAG report states that: "Furthermore, regarding the OS of the RET fusion-positive TC population, Table 4.10 and Table 4.11 as well as the electronic model include 17 different parametric models, with the stratified spline 1/2/3 knot models missing, while those are still part of Table 4.9 where the AIC/BIC scores for all 20 models are reported."	Please can this statement be removed.	The extrapolations were excluded from the cost-effectiveness model as the spline knot model with three knots did not converge, while the spline knot models with one and two knots predicted increasing survival for selpercatinib over time, and were therefore not deemed plausible.	This was not a factual error as the explanation provided here was not part of the submission. However, in light of the explanation we have removed the statement and added to table 4.9 in the key: *[a]The stratified spline/knot 3 model did not converge* and in the text below that table: *(the stratified 1 knot and 2 knot spline curves were omitted as these showed increasing survival over time),*

Issue 10 Clinical plausibility of OS extrapolations in the *RET* fusion-positive TC population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135, Section 4.2.6.4 of the EAG report states that: "Based on the clinical plausibility criterion the stratified gamma or stratified Weibull would get closer to the estimates provided by the clinical experts for selpercatinib and BSC, without the need to implement adjustment factors for selpercatinib (Table 4.10 above)."	Please include a statement here as follows: **"The EAG acknowledges that alternative extrapolations, such as the stratified gamma or stratified Weibull would predict survival rates at 10 years that fall under the plausible range given by clinicians, without the application of an adjustment factor."**	As per Table 4.10 of the EAG report, the stratified Weibull and stratified gamma extrapolations predict rates of survival at 10 years that fall under the plausible limit estimated by clinicians. Thus, without the application of an adjustment factor, these extrapolations do not fall within plausible ranges predicted by clinicians. This fact is currently omitted in this section of the EAG report. The piecewise exponential extrapolation with a 1.2 adjustment factor applied falls within plausible limits predicated by clinicians at both 10 years and 20 years.	This is not a factual error, though the EAG does agree that the comment is somewhat imprecise. Thus, this comment is now replaced by the following: "Based on the clinical plausibility criterion, the piecewise model provided a 10-year OS within the range predicted by clinical experts, but the estimated 20-year survival was above the predicted range. The stratified gamma or stratified Weibull predicted 10-year OS below the predicted range, while at 20 years within the range. The EAG thinks that although use of these options would be slightly more pessimistic in terms of 10-year OS, it would not require application of any adjustment factors for selpercatinib to force both 10-year and 20-year OS to fall within the experts' range (Table 4.10 above).

Typographical Errors

Issue 11 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, Section 3.1.1 of the EAG report states that: "Conference proceedings were searched (2019, 2020, 2022 & 2023)"	Please can the text be amended to: "Conference proceedings **from 2019−2023** were searched."	Typographical error. The statement should be amended to clarify that conference proceedings from the stated years were searched. The year 2021 should also be included here so that the new statement is correct, as per Page 31, Appendix D1.1.	This correction has been made.
Page 66, Section 3.2.5.2.2 of the EAG report states that: **"EAG comment:** The EAG notes that, at the DCO, [redacted] any-line *RET* fusion-positive TC population were alive without documented disease progression by IRC assessment, compared to [redacted] prior systemic therapy *RET* fusion-positive TC population and [redacted] in the population who had received prior lenvatinib or sorafenib."	Please can the text be amended to: **EAG comment:** The EAG notes that, at the DCO, [redacted] **65** [redacted] any-line *RET* fusion-positive TC population were alive without documented disease progression by IRC assessment, compared to [redacted] **41** [redacted] prior systemic therapy *RET* fusion-positive TC population and [redacted] in the population who had received prior lenvatinib or sorafenib.	Typographical error. The number of patients reported in prior systemic therapy *RET* fusion-positive TC population is incorrect. As stated in Table 28, page 85, Section of B.2.6.2 of the CS, the correct number of patients in the prior systemic therapy *RET* fusion-positive TC population is 41. Furthermore, the number of patients in the any-line *RET* fusion-positive TC (N=65) and the prior systemic therapy *RET* fusion-positive TC (N=41) populations has been published. As such, the confidentiality highlighting can be removed.	These corrections have been made.
Page 77, Section 3.2.5.5.1 of the EAG report states that:	Please can the text be amended to remove 'between', in addition to incorporating the following changes in red:	Typographical error. The difference reported in duration of response rates between the	This text has been amended to specify

"EAG comment: The EAG notes that the proportions of patients in response for ≥12 months, ≥24 months, and ≥36 months, were consistently [redacted] in the *RET*-mutant MTC any-line population than in the prior cabozantinib/vandetanib population, with a difference of between [redacted] and [redacted] or in the prior cabozantinib or vandetanib population, with a difference of between [redacted] and [redacted]"	**EAG comment:** The EAG notes that the proportions of patients in response for ≥12 months, ≥24 months, and ≥36 months, were consistently [redacted] in the *RET*-mutant MTC any-line population than in the prior cabozantinib/vandetanib population, with a difference of between [redacted] and [redacted] or in the prior cabozantinib or vandetanib population, with a difference of [redacted] and [redacted], **for ≥12 and ≥24 months, respectively.**	*RET*-mutant MTC any-line population and the prior cabozantinib/vandetanib population at ≥24 months is incorrect. This difference is calculated using the proportions of patients in response for ≥24 months, which were [redacted] and [redacted], respectively, as presented in Table 21, Page 72, Section B.2.6.1 of the CS. Therefore, this difference is [redacted]. The specific timepoints that these differences correspond to should also be reported, for clarity.	the individual time points.
Page 79, Section 3.2.5.5.2 of the EAG report states that: "For the prior systemic therapy *RET* fusion-positive TC population, after a median follow-up of 33.9 months, the median DOR by IRC was 26.7 months (95% CI: 12.1, NE),[5] and for the prior lenvatinib or sorafenib *RET* fusion-positive TC population, after a median follow-up of [redacted] months, the median DOR by IRC was [redacted] months [redacted]."	Please can the text be amended to: For the prior systemic therapy *RET* fusion-positive TC population, after a median follow-up of 33.9 months, the median DOR by IRC was 26.7 months (95% CI: 12.1, NE),[5] and for the prior lenvatinib or sorafenib *RET* fusion-positive TC population, after a median follow-up of [redacted] months, the median DOR by IRC was [redacted] months [redacted].	Typographical error. The median duration of response (DOR) assessed by the independent review committee (IRC) reported for the prior lenvatinib or sorafenib *RET* fusion-positive TC population is incorrect. The correct data are reported in Table 14, Page 24, in the company response to clarification questions.	This correction has been made.
Table 3.27, Page 82, Section 3.2.6.1 of the EAG report presents the following data for objective response rate (ORR) and DOR by number of prior therapies:	Please can this be amended to: **Number of prior therapies** 1 [redacted] 2 [redacted] 3 or more [redacted]	Typographical error. These data correspond to subgroup analyses by prior systemic therapy for the prior systemic therapy *RET* fusion-positive TC population, rather than	These corrections have been made.

Number of prior therapies 1 [redacted] 2 [redacted] 3 or more [redacted]		the prior cabozantinib/vandetanib *RET*-mutant MTC population. The correct data are presented in Table 34, Section B.2.7.1 of the CS. Please note that the reference to the CSR provided in the footnote of this table is however correct.	
Page 88, Section 3.2.6.2 of the EAG report states: "However, it should be noted that (within the small numbers of patients with cancer types other than PTC) ORRs were generally high; [redacted]/4 patients with ATC, and [redacted] patients with Hürthle cell TC (n=1) or poorly differentiated TC (n=6)."	Please clarify which patient population (any-line *RET* fusion-positive TC or prior systemic therapy *RET* fusion-positive TC) is being referred to in this summary. If the prior systemic therapy *RET* fusion-positive TC population is being referred to, please can the text be amended to: However, it should be noted that (within the small numbers of patients with cancer types other than PTC) ORRs were generally high; [redacted]/4 patients with ATC, and [redacted] patients with Hürthle cell TC (n=1) or poorly differentiated TC (n=5).	Potential typographical error. The patient population these data are being presented for should be clarified; there are 6 patients with poorly differentiated TC in the any-line population and 5 patients in the prior systemic therapy population (as per Table 10, Page 51 of the CS). ORR data by *RET* fusion type are presented in Table 17, Page 27 in the company response to clarification questions.	This correction has been made and the population clarified.
Table 3.32, Page 89, Section 3.2.6.2 of the EAG report presents the following subgroup analyses for ORR and DOR based on prior multikinase inhibitor (MKI) treatment: Yes [redacted]	Please can this be amended to: Yes [redacted]	Typographical error. The correct 95% confidence intervals (CIs) associated the median DOR for patients that received prior kinase inhibitor therapy within the prior systemic therapy *RET* fusion-positive TC population is presented in Table 14.2.7.1, Page 906 of the CSR.[3]	This correction has been made.
Page 94, Section 3.2.7.1 of the EAG report states that:	Please can the text be amended to: Adverse events led to dose reductions in [redacted] of *RET*-mutant MTC, [redacted] of *RET* fusion-positive TC,	Typographical error. These data correspond to dose reductions due to any reason,	These corrections have been made.

"Adverse events led to dose reductions in [redacted] of *RET*-mutant MTC, [redacted] of *RET* fusion-positive TC, and [redacted] of OSAS patients, and dose interruptions in [redacted], and [redacted] of these groups, respectively."	and [redacted] of OSAS patients, and dose interruptions in [redacted] and [redacted] of these groups, respectively.	rather than dose reductions specifically attributed to adverse events (AEs). The correct data (dose reductions due to AEs) are reported in Table 46, Page 120, Section B.2.10.1 of the CS and Table 27, Page 99, Appendix F.1 of the CS, respectively.	
Page 97, Section 3.2.7.3 of the EAG report states that: "While the prevalence of certain AEs varied between groups, such as hypertension being more common in *RET*-mutant MTC patients and diarrhoea in *RET* fusion-positive TC patients, others like AST increase were consistent across all populations."	Please can the text be amended to: "While the prevalence of certain AEs varied between groups, such as **Grade ≥3** hypertension being more common in *RET*-mutant MTC patients and diarrhoea in *RET* fusion-positive TC patients, others like **rash** were consistent across all populations."	Potential typographical error While rates of Grade ≥3 hypertension are higher in the *RET*-mutant MTC population, rates of any grade hypertension AEs are higher in the *RET* fusion-positive TC population, as displayed in Table 3.41 of the EAG report. This should be clarified. Furthermore, the EAG may wish to reconsider their chosen example for AEs with consistent rates across the *RET*-altered TC and MTC populations, as rates of any grade aspartate aminotransferase (AST) increases illustrated in this table vary between the two populations.	These corrections have been made.
Page 102, Section 3.3.1 of the EAG report states that: "However, it is true that only 40% patients in ZETA were known to be mutation positive and so the EAG does agree that EXAM was	Please clarify the source used for this datapoint and consider revising this estimate if incorrect.	Potential typographical error. It is unclear what source has been used to report the proportion of mutation positive patients in the ZETA trial.	Corrected.

possibly the more appropriate of two trials considered." 		According to the Wells et al. 2012 publication, 137/231 (59.3%) patients in the vandetanib arm and 50/100 (50.0%) patients in the placebo arm were *RET* mutation-positive.[5]	
Page 110, Section 4.13 of the EAG report states that: "The sum of the in- and excluded studies is 68 studies, far less than the 292 studies that were included according to the PRISMA diagram. This raises the question whether the remaining HRQoL and cost and resource use studies shown as included in the PRISMA diagrams all pertain to NSCLC, or that another reason exists for this discrepancy."	Please can this statement be removed.	Inaccurate statement. It is clearly stated in the figure caption for Figure 3 in the Appendices (Page 116) that the PRISMA diagram presents the number of included and excluded studies for economic evaluation in **both** non-small cell lung cancer (NSCLC) and TC. In total, there were 34 studies included across the economic and health-related quality of life (HRQoL) searches for thyroid cancer (Table 40 and Table 42 in the Appendices), and 34 studies excluded (Table 41 in the Appendices). The remaining studies therefore pertain to NSCLC. Thus, there is no discrepancy to raise here, given that the PRISMA diagram is clearly labelled for both NSCLC and thyroid cancer searches.	This is not a factual error. From the EAG comment it is clear that they recognised that the numbers in the PRISMA diagram were for TC and NSCLC together. However, in a submission for a TC population it would have made more sense to present the numbers of in- and excluded studies for TC only or additionally. In absence of that information, the remark from the company that '*The remaining studies **therefore** pertain to NSCLC*.' was not a forgone conclusion for the EAG. We have changed the comment to:

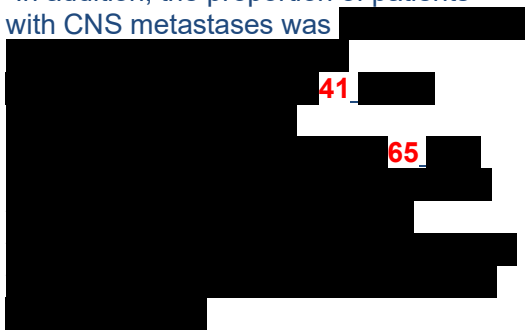
			This raised the question whether the remaining HRQoL and cost and resource use studies shown as included in the PRISMA diagrams all pertain to NSCLC, this was later confirmed by the company to be so.
Page 129, Section 4.2.6.3 of the EAG report states that Table 4.10 is based on Table 49 of the CS in the footnote.	Please can the footnote be amended to: "Based on **Table 67** of the CS and **response to Question B.3.e of the clarification questions (Table 49)**"	An incorrect table number is referenced in the footnote relevant to the CS, and the reference to the updated table presented in the clarification question responses is missing.	This has been corrected
Page 130, Section 4.2.6.3 of the EAG report states that Table 4.11 is based on Table 62 of the CS in the footnote.	Please can the footnote be amended to: "Based on **Table 68** in the CS"	An incorrect table number is referenced in the footnote for the CS.	This has been corrected
Table 4.15, Pages 137 and 138, Section 4.2.7 of the EAG report presents the incidence of Grade 3 or 4 AEs included in the model for the *RET*-mutant MTC population that were reported in ≥2% of patients. However, some AEs are missing from the table, and one AE is incorrectly included.	Please can Table 4.15 be amended to include: "**Fatigue: 3.70% (selpercatinib), 2.75% (BSC)**" "**Dyspnoea: [redacted] (selpercatinib), 0.00% (BSC)**" "**Headache: 2.78% (selpercatinib), 10.09% (BSC)**" **and** Please can the following row be removed from the table: "Haemorrhage: [redacted] (selpercatinib), 0.92% (BSC)"	Table 4.15 is missing incidence of fatigue, dyspnoea and headache AEs. These AEs should be presented in this table, given that they were reported by ≥2% of patients in either the selpercatinib or BSC populations, as reported in Table 71 (Page 164) of Document B of the CS. Haemorrhage AE should be removed from the table, given that this was reported by <2% of	This has been corrected

		patients for both the selpercatinib and BSC populations.	
Page 142, Section 4.2.9.1.1 of the EAG report states that: "In the first period, the cost per week is £708.68, totalling £2,834.71 for four weeks"	Please can this statement be amended to: "**For MTC**, in the first period the cost per week is £708.68, totalling £2,834.71 for four weeks" **and** Please can the following statement be added: "**For TC, in the first period the cost per week is £733.36, totalling £2933.43 for four weeks**"	The original statement should be amended to specify that these are the costs for the MTC population, and a statement should be added to present the corresponding costs for the TC population, for clarity.	This has been added
Page 142, Section 4.2.9.1.1 of the EAG report states that: "In the subsequent treatment periods, the cost per week is £600, totalling £2,400 for four weeks"	Please can this statement be amended to: "**For MTC**, in the subsequent treatment periods the cost per week is [redacted], totalling [redacted] for four weeks" **and** Please can the following statement be added: "**For TC, in the subsequent treatment periods, the cost per week is [redacted], totalling [redacted] for four weeks**"	The original statement should be amended to specify that these are the costs for the MTC population in the subsequent treatment periods, and a statement should be added to present the corresponding costs for the TC population, for clarity. Costs in the subsequent treatment periods should also be presented to two decimal places here, for consistency with costs presented throughout the report.	This has been changed
Page 146 (Table 4.25), Section 4.2.10 of the EAG report reports the absolute quality-adjusted life year (QALY) shortfall for the *RET*-mutant MTC population as 12.51.	Please can the value for the absolute QALY shortfall for the *RET*-mutant MTC population be amended to **14.02.**	This value should be corrected to align with the value reported in Table 86, Section B.3.6 of Document B of the CS.	We have not corrected this value, as the value in Table 86 is most likely a typo. Instead, we now write in the key to the table: *Based on Table 86 of the CS, with a correction for the absolute QALY shortfall for MTC,*

			as this value was 14.02 in Table 86 of the CS, the same as the expected total QALYs for the general population.
Page 148 (Table 5.3), Section 5.1.1 of the EAG report reports the total absolute increment for the *RET* fusion-positive TC population to be [redacted]	Please can the value for the total absolute increment for the *RET* fusion-positive TC population be amended to [redacted]	This value should be amended to be equal to the total of the absolute increment column in Table 5.3 of the EAG report for the *RET* fusion-positive TC population.	Correction was made.

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 2.1, Page 24, Section 2.	The Patient Access Scheme (PAS) discount for selpercatinib is confidential. As such, confidentiality highlighting should be used for this value.	Please can confidentiality highlighting be added as follows: "**Commercial arrangements:** A confidential Patient Access Scheme (PAS) of [redacted] has been provided alongside this submission."	Confidentiality marking has been applied, as indicated.
Page 45, Section 3.2.2.1.	The number of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC and the any-line *RET*-mutant MTC populations do not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can the confidentiality highlighting be removed as follows: "Of the 152 patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population, [redacted]**152**[redacted] were still on treatment as of the 13 January 2023 DCO, a lower proportion than was the case for the any-line *RET*-mutant MTC population, [redacted]**295** [redacted] of whom were	Confidentiality marking has been removed, as indicated.

		still on treatment as of the 13 January 2023 DCO."	
Page 46, Section 3.2.2.2.	The number of patients in the prior systemic therapy *RET* fusion-positive TC and the any-line *RET* fusion-positive TC populations do not need to be marked a confidential, as these data are published. As such, the confidentiality highlighting can be removed.	Please can the confidentiality highlighting be removed as follows: "Of the 41 patients in the prior systemic therapy *RET* fusion-positive TC population, [redacted]**41**[redacted] were still on treatment as of the 13 January 2023 DCO, a lower proportion than was the case for the any-line *RET* fusion-positive TC population, [redacted]**65**[redacted] of whom were still on treatment as of the 13 January 2023 DCO."	Confidentiality marking has been removed, as indicated.
Page 51, Section 3.2.3.2.	The number of patients in the prior systemic therapy *RET* fusion-positive TC and the any-line *RET* fusion-positive TC populations do not need to be marked a confidential, as these data are published. As such, the confidentiality highlighting can be removed. Please also highlight statements based on confidential data, including the latter half of this sentence here.	Please can the confidentiality highlighting be removed as follows: "In addition, the proportion of patients with CNS metastases was [redacted]  [redacted]**41**[redacted]**65**[redacted]	Confidentiality marking has been amended, as indicated.
Page 57, Section 3.2.5.1.1.	The ORR for patient with *RET*-mutant MTC who had received prior cabozantinib/vandetanib does not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can confidentiality highlighting be removed as follows: "For patients with *RET*-mutant MTC who had received prior cabozantinib/vandetanib, ORR was **77.6%** [redacted]/152, 95% CI: 70.2, 84.0), with	Confidentiality marking has been removed, as indicated.

		19/152 (12.5%) of patients achieving CR and 99/152 (65.1%)"	
Page 57, Section 3.2.5.1.1.	The number of patients in the any-line *RET*-mutant MTC population does not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can confidentiality highlighting be removed as follows: "**EAG comment:** The EAG notes that the ORR was [redacted] in the *RET*-mutant MTC any-line population, [redacted]**295** [redacted] than in the RET-mutant MTC prior cabozantinib/vandetanib population, [redacted]152 [redacted], though [redacted] to that provided for the RET-mutant MTC prior cabozantinib or vandetanib population, [redacted]. The EAG further notes that a [redacted] proportion of patients in the *RET*-mutant MTC any-line population, [redacted]**295** [redacted], achieved a BOR category of CR than in the *RET*-mutant MTC prior cabozantinib/vandetanib population or the RET-mutant MTC prior cabozantinib or vandetanib population."	Confidentiality marking has been removed, as indicated.
Page 60, Section 3.2.5.1.2.	The number of patients in the any-line *RET* fusion-positive TC population does not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can confidentiality highlighting be removed as follows: "**EAG comment:** The EAG notes that the ORR was [redacted] in the *RET* fusion-positive TC any-line population, [redacted]**65** [redacted] than that seen in the *RET* fusion-positive prior systemic therapy population and in the *RET* fusion-positive TC population who had received prior lenvatinib **or** sorafenib. The EAG further notes that a [redacted] proportion of patients in the *RET* fusion-positive TC any-line population, [redacted]**65** [redacted], achieved a BOR category of CR than in the *RET* fusion-positive prior systemic therapy population	Confidentiality marking has been removed, as indicated.

		and in the *RET* fusion-positive TC population who had received prior lenvatinib or sorafenib."	
Page 62, Section 3.2.5.2.1.	The median duration of follow-up for progression-free survival (PFS) for patients with *RET*-mutant MTC who had received prior cabozantinib or vandetanib has not been published. As such, confidentiality highlighting should be used for these data.	Please can confidentiality highlighting be added as follows: "For patients with *RET*-mutant MTC who had received prior cabozantinib or vandetanib (in-line with the decision problem), after a median duration of follow-up of [redacted] months, median PFS was [redacted] months (95% CI: [redacted])."	Confidentiality marking has been applied, as indicated.
Page 62, Section 3.2.5.2.1. Page 68, Section 3.2.5.3.1.	The number of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC and the any-line *RET*-mutant MTC populations do not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can confidentiality highlighting be removed as follows: **"EAG comment:** The EAG notes that, at the DCO, [redacted]295 [redacted] of patients in the any-line *RET*-mutant MTC population were alive without documented disease progression by IRC assessment, compared to [redacted]152 [redacted] of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population and [redacted] of patients in the prior cabozantinib or vandetanib *RET*-mutant MTC population." Please can confidentiality highlighting be removed as follows: **"EAG comment:** The EAG notes that, at the DCO, [redacted]295 [redacted] of patients in the any-line *RET*-mutant MTC population were alive or lost to follow-up, compared to [redacted]152 [redacted] of patients in the prior cabozantinib/vandetanib *RET*-mutant	Confidentiality marking has been removed, as indicated.

		MTC population and [redacted] in the prior cabozantinib or vandetanib *RET*-mutant MTC population."	
Page 70, Section 3.2.5.3.2.	The number of patients in the prior systemic therapy *RET* fusion-positive TC and the any-line *RET* fusion-positive TC populations do not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can confidentiality highlighting be removed as follows: **EAG comment:** The EAG notes that, at the DCO, [redacted]65 [redacted] of patients in the any-line *RET* fusion-positive TC population were alive or lost to follow-up, compared to [redacted]41 [redacted] of patients in the prior systemic therapy *RET* fusion-positive TC population and [redacted] of patients in the prior lenvatinib or sorafenib *RET* fusion-positive TC population.	Confidentiality marking has been removed, as indicated.
Page 77, Section 3.2.5.5.1.	The median duration of follow-up for DOR for patients in the any-line *RET*-mutant MTC population has not been published. As such, confidentiality highlighting should be used for these data.	Please can confidentiality highlighting be added as follows: "After a median follow-up of [redacted] months, the median DOR was [redacted] in the *RET*-mutant MTC any-line population."	Confidentiality marking has been applied, as indicated.
Page 82, Section 3.2.6.1.	The number of patients in the prior cabozantinib/vandetanib *RET*-mutant MTC population does not need to be marked a confidential as these data are published. As such, the confidentiality highlighting can be removed.	Please can confidentiality highlighting be removed as follows: "The EAG notes that prior treatment with both cabozantinib and vandetanib occurred in [redacted]152 [redacted] of prior cabozantinib/vandetanib *RET*-mutant MTC population in the LIBRETTO-001 study and appeared to be associated with a [redacted] ORR than prior treatment with either cabozantinib or vandetanib alone."	Confidentiality marking has been removed, as indicated.
Table 3.41, Page 97, Section 3.2.7.3.	The number and proportion of patients within the overall safety analysis set (OSAS) experiencing (Grade ≥3)	Please can confidentiality highlighting be removed as follows:	Confidentiality marking has been removed, as indicated.

<table>
<tr>
<td></td>
<td>diarrhoea, constipation, nausea, vomiting, arthralgia, back pain and decreased appetite have been published. As such, confidentiality highlight may be removed for these data.</td>
<td>
<table>
<tr><th>Preferred term</th><th>Any grade</th><th>Grade ≥3</th></tr>
<tr><td>Diarrhoea</td><td>[redacted]</td><td>49 (5.9)</td></tr>
<tr><td>Constipation</td><td>295 (35.2)</td><td>7 (0.8)</td></tr>
<tr><td>Nausea</td><td>289 (34.5)</td><td>14 (1.7)</td></tr>
<tr><td>Vomiting</td><td>226 (27.0)</td><td>20 (2.4)</td></tr>
<tr><td>Arthralgia</td><td>192 (22.9)</td><td>3 (0.4)</td></tr>
<tr><td>Back pain</td><td>187 (22.3)</td><td>17 (2.0)</td></tr>
<tr><td>Decreased appetite</td><td>185 (22.1)</td><td>7 (0.8)</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Table 3.42, Page 98, Section 3.2.7.4.</td>
<td>The number and proportion of patients within the OSAS experiencing Grade 3–4 diarrhoea and vomiting have been published. As such, confidentiality highlighting may be removed for these data.</td>
<td>Please can confidentiality highlighting be removed as follows:
<table>
<tr><th>Preferred term</th><th>OSAS (N=837)</th></tr>
<tr><td>Diarrhoea</td><td>49 (5.9)</td></tr>
<tr><td>Vomiting</td><td>20 (2.4)</td></tr>
</table>
</td>
<td>Confidentiality marking has been removed, as indicated.</td>
</tr>
<tr>
<td>Page 136, Section 4.2.6

Page 155 (Table 5.7), Section 5.3.2

Page 167, Section 6.4</td>
<td>The mean time from progression to treatment discontinuation for patients in the previously treated RET-mutant MTC and RET fusion-positive TC populations used in the economic model are sourced from unpublished data from the LIBRETTO-001 trial. As such, these data should be marked as confidential.</td>
<td>Please can confidentiality highlighting be added as follows for Page 136 and 167:

“Time to treatment discontinuation (TTD) in the selpercatinib arm, for both the RET-mutant MTC and RET fusion-positive TC populations, was set equal to PFS, with the addition of the mean time from progression to treatment discontinuation, as observed in the previously treated RET-mutant MTC and the previously treated RET fusion-positive TC populations ([redacted] for MTC and [redacted] for TC).”

and</td>
<td>Confidentiality marking has been applied, as indicated.</td>
</tr>
</table>

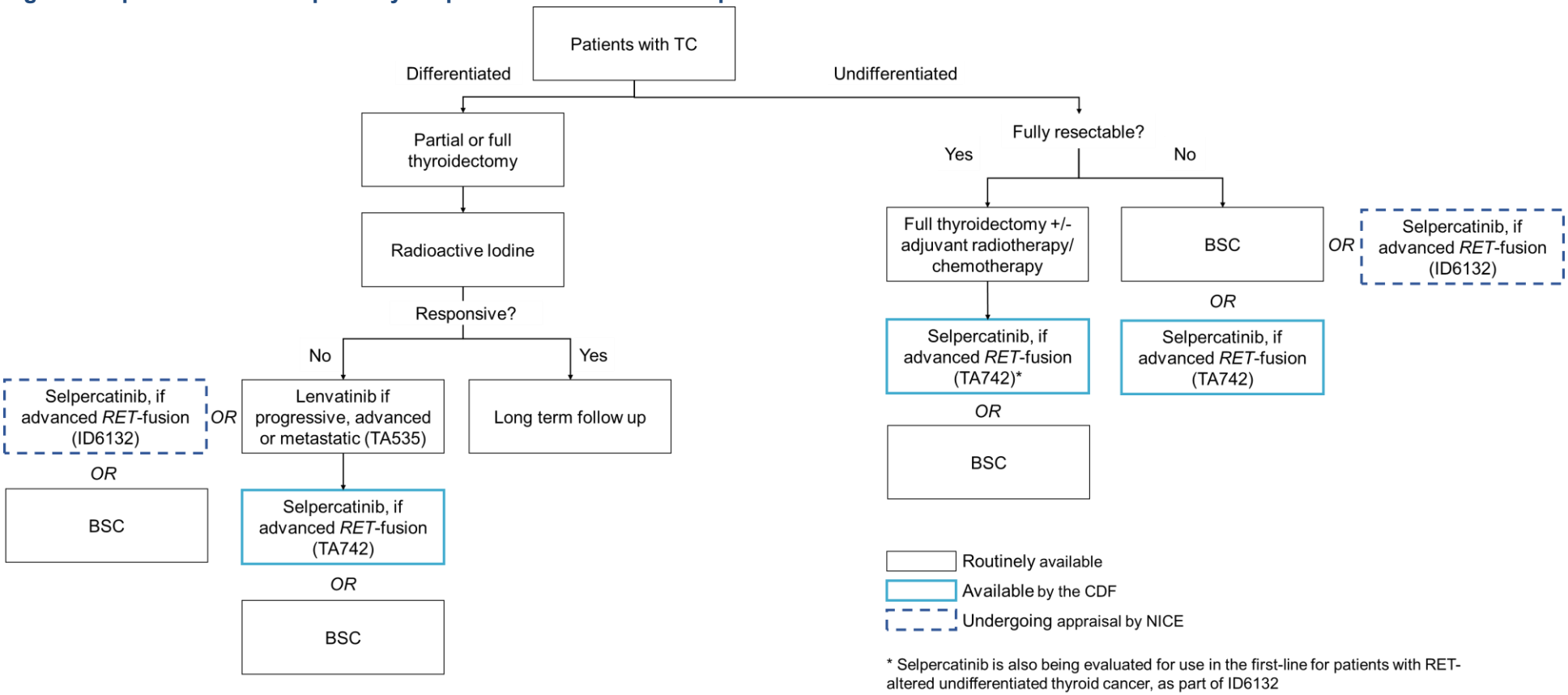
		Please can confidentiality highlighting be added for Page 155, Table 5.7 as follows: "Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted]" for *RET*-mutant MTC "Selpercatinib TTD is assumed equal to PFS, with a delay of [redacted]" for *RET* fusion-positive TC"	
Page 140 (Table 4.18), Section 4.2.8.2 presents health state utility value data derived from the LIBRETTO-001 trial for the *RET* fusion-positive TC population	Health state utility values used in the economic model for the progression-free and progressed health states are derived from unpublished data from the LIBRETTO-001 trial. As such, these values should be marked as confidential.	Please can confidentiality highlighting be added as follows: "[redacted]"|"[redacted]"	Confidentiality marking has been applied, as indicated.
Page 142, Section 4.2.9.1.1	Costs for selpercatinib in the subsequent treatment periods are confidential and therefore these values should be highlighted.	Please can confidentiality highlighting be added as follows: "**For MTC**, in the subsequent treatment periods the cost per week is [redacted], totalling [redacted] for four weeks" The statement should also be amended to specify that these are the costs for MTC in the subsequent treatment periods, and a statement should be added to present the corresponding costs for TC for clarity, as follows: "**For TC, in the subsequent treatment periods, the cost per week is [redacted], totalling [redacted] for four weeks**" Costs in the subsequent treatment periods should also be presented to two	Confidentiality marking has been applied and corrections made, as indicated.

		decimal places here, for consistency with costs presented throughout the report.	

Appendix A: Treatment pathway for patients with *RET* fusion-positive TC

An updated treatment pathway diagram for patients with *RET* fusion-positive TC is provided by Figure 1.

Figure 1: Updated treatment pathway for patients with *RET* fusion-positive TC



Abbreviations: BSC: best supportive care; CDF: Cancer Drug's Fund; NICE: National Institute of Health and Care Excellence; RET: rearranged during transfection; TA: technology appraisal; TC: thyroid cancer.

Appendix B: Complete list of included studies in the clinical SLR

Table 1: Study characteristics for included studies

Trial Name, Author (Year) Country	Trial Characteristics	Inclusion Criteria	Exclusion Criteria	Intervention (N)	Treatment dosage and Schedule	Tumour type
ARROW Subbiah *et al.* (2021) Multinational	Phase I/II, open-label, single arm	• Diagnosis during dose escalation (Phase I) - Pathologically documented, definitively diagnosed non-resectable advanced solid tumor. • All participants treated at doses > 120 mg per day must have MTC, or a RET-altered solid tumor per local assessment of tumor tissue and/or blood. • Diagnosis during dose expansion (Phase II) - All participants (with the exception of participants with MTC enrolled in Groups 3, 4, and 9) must have an oncogenic RET-rearrangement/fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumor, as determined by local or central testing of tumor or circulating tumor nucleic acid in blood • Participants must have non-resectable disease.	• Cancer with a known primary driver alteration other than RET. For example, NSCLC with a targetable mutation in EGFR, ALK, ROS1 or BRAF; colorectal with an oncogenic KRAS, NRAS, or BRAF mutation. • Participants had any of the following within 14 days prior to the first dose of study drug: ○ Platelet count < 75 × 10^9/L. ○ Absolute neutrophil count < 1.0 × 10^9/L. ○ Hemoglobin < 9.0 g/dL (red blood cell transfusion and erythropoietin may be used to reach at least 9.0 g/dL, but must have been administered at least 2 weeks prior	Pralsetinib (N=122)	30−600mg oral pralsetinib QD or BID (Phase I) 400mg oral pralsetinib QD (Phase II)	MTC

		• Dose expansion (Phase 2): Participants in all groups (except Group 7) must have measurable disease per RECIST v1.1 (or RANO, criteria if appropriate for tumor type). • Participants agrees to provide tumor tissue (archived, if available or a fresh biopsy) for RET status confirmation and is willing to consider an on-treatment tumor biopsy, if considered safe and medically feasible by the treating Investigator. For Phase II, Group 6, participants are required to undergo a pretreatment biopsy to define baseline RET status in tumor tissue. • Participants has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.	to the first dose of study drug. ○ Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present. ○ Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease. ○ Estimated (Cockcroft-Gault formula) or measured creatinine clearance < 40 mL/min. ○ Total serum phosphorus > 5.5 mg/dL • QT interval corrected using Fridericia's formula (QTcF) > 470 msec or history of prolonged QT syndrome or Torsades de pointes, or			

			familial history of prolonged QT syndrome. • Clinically significant, uncontrolled, cardiovascular disease. • Central nervous system (CNS) metastases or a primary CNS tumor that is associated with progressive neurological symptoms. • Clinically symptomatic interstitial lung disease or interstitial pneumonitis including radiation pneumonitis • Participants in Groups 1-5 and 7 (Phase 2) previously treated with a selective RET inhibitor • Participant had a major surgical procedure within 14 days of the first dose of study drug • Participant had a history of another primary malignancy that had been diagnosed or required therapy within the a year prior to the study • Pregnant or breastfeeding female participants			
COSMIC-311 Brose *et al.* (2021)	Phase III, double-blind RCT	• Histologically or cytologically confirmed diagnosis of Differentiated Thyroid Cancer (DTC) • Measurable disease	• Prior treatment with any of the following: Cabozantinib; Selective small-molecule v-raf murine sarcoma viral oncogene homolog B1	Cabozantinib (N=125)	Oral 60mg or 20mg cabozantinib QD	DTC

Multinational		according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Previously treated with or deemed ineligible for treatment with Iodine- 131 for DTC • Previously treated with at least one of the following vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitor (TKI) agents for DTC: lenvatinib or sorafenib. Note: Up to two prior VEGFR-targeting TKI agents are allowed • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1	(BRAF) kinase inhibitor; More than 2 VEGFR-targeting TKI agents; More than 1 immune checkpoint inhibitor therapy; 1 systemic chemotherapy regimen (given as single agent or in combination with another chemotherapy agent) • Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer, before randomization • Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization • Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization. • Known brain metastases or cranial epidural disease unless adequately treated			
D4200C00088 Bastholt (2016)	Phase III, open-label, parallel- group RCT	• Aged ≥18 years , with a histologically confirmed diagnosis of unresectable, locally advanced, or metastatic hereditary or	• Unstable brain metastases. • Major surgery within 4 weeks before randomisation.	Vandetanib + outreach programme (N = 102)	• Patients with a screening CrCl ≥ 50 ml/min started vandetanib at	MTC

Multinational		sporadic MTC. • Performance status of 0–2 (ECOG). • Negative PT.	• The last dose of prior chemotherapy received less than 3 weeks prior to randomisation. • RT not completed prior to the first dose of vandetanib. • Significant cardiac event. • CrCl < 30 ml/min.	Vandetanib (N = 102)	300 mg (3× 100-mg tablets) QD. • Patients with a screening CrCl ≥ 30 to < 50 ml/ min, started vandetanib at a reduced dose of 200 mg QD (2×100-mg tablets). • The starting dose was administered throughout this study unless a dose reduction was required. • Patients were contacted by study site personnel Q2W to detect and possibly treat AEs at an earlier time point than would be possible without patient outreach. • In addition, at randomisation, patients in the outreach arm were given a	

					patient information card and a rescue package that consisted of loperamide for treatment of diarrhoea and sunscreen for prevention of skin conditions.	
D4200C00079 Leboulleux (2012) Multinational	Phase II, double-blind, parallel-group RCT	• Aged ≥18 years with histologically confirmed locally advanced (surgically unresectable) or metastatic DTC. • Target lesions according to RECIST version 1.018. • Unsuitable for radioiodine therapy. • Serum TSH concentrations of less than the normal reference range (< 0.5 mIU/L). • WHO PS of ≤ 2. • Normal cardiac, haematological, hepatic, and renal function. • Patients with brain metastases were eligible if their treatment had stopped ≥ 4 weeks before the date of randomisation. • Presence of ≥ 1 measurable lesions ≥ 1 cm in the longest	• Chemotherapy or RT (apart from palliative therapy) within the 4 weeks before date of randomisation • Unresolved toxicity (CTCAE grade >1) from previous anticancer treatment. • Previous exposure to vandetanib. • Major surgery within 4 weeks before randomisation. • RAI131 therapy within 3 months in patients with radioiodine uptake. • Clinically significant CV event within 3 months before entry.	Vandetanib (N = 72)	300 mg vandetanib QD orally	DTC including PTC subpopulation
				Placebo (N = 73)	Matching placebo once daily	

		diameter. • Progressive disease following RAI131 or patient unsuitable for RAI131 after surgery.				
D4200C00097 Hu (2019) Multinational	Phase IV, double-blind, Parallel-group RCT	• Adults aged ≥ 18 years with histologically confirmed, unresectable, locally advanced, or metastatic, hereditary, or sporadic MTC. • Objective disease progression. • WHO status of 0 to 2. • Has measurable disease (≥ 1 lesion, not irradiated within 12 weeks of study randomisation. • Lesions must be amenable to accurate and repeat measurement.	• Significant cardiac, hematopoietic, hepatic, or renal dysfunction. • Prior treatment (major surgery, RT, chemotherapy, or other investigational drugs) received within 28 days before randomisation. • Abnormal LFTs. • Significant cardiac conditions or event. • Abnormal electrolytes. • Currently pregnant or breast feeding.	Vandetanib 150 mg (N = 40)	Oral Vandetanib 150 mg QD during the DB treatment period	MTC
				Vandetanib 300 mg (N = 41)	Oral Vandetanib 300 mg QD during the DB treatment period	
				Vandetanib 150 mg → Vandetanib 100 mg (N = 5)	Oral vandetanib 150 mg QD during the DB treatment period → oral vandetanib 100 mg QD during the OL treatment period	
				Vandetanib 150 mg throughout (N = 9)	Oral vandetanib 150 mg QD during both treatment periods	
				Vandetanib 150/300 mg → Vandetanib 300 mg (N = 39)	Oral vandetanib 150 or 300 mg QD during the DB treatment period → oral vandetanib 300 mg QD during the OL treatment period	
				Vandetanib 300 mg →	Oral vandetanib 300 mg QD during the DB treatment	

				Vandetanib 200 mg (N = 8)	period → oral vandetanib 200 mg QD during the OL treatment period	
DECISION Brose (2014) Multinational	Phase III, double-blind, parallel-group RCT	• Age ≥ 18 years; locally advanced or metastatic RAI-refractory DTC progressing within the past 14 months according to RECIST. • ≥ 1 measurable lesion • ECOG PS 0–1. • Adequate bone marrow, liver, and renal function; and serum. • TSH < 0.5mIU/L. • Women of childbearing potential must have a negative serum PT performed within 7 days prior to the start of treatment. • Subjects must be able to swallow and retain oral medication.	• Patients who had received prior targeted therapy, thalidomide, or chemotherapy for thyroid cancer. • Histologic subtypes of thyroid cancer other than differentiated • Prior anti-cancer treatment with TKI's, mAbs (licensed or investigational) that target VEGF or VEGF receptors or other targeted agents. • Major surgery 30 days prior to randomisation. • Clinically significant cardiac disease. hypersensitivity to • Subjects undergoing renal dialysis. • History of brain metastases: allowed, provided definitive therapy (surgery and/or radiation) has been administered before randomisation, no further treatment of brain metastases is planned, the subject is clinically stable for at least 2 weeks before study treatment.	Sorafenib	Sorafenib 400 mg, given orally BID.	DTC including PTC subpopulation
				Placebo	Matching placebo, given orally BID.	
				Sorafenib → Sorafenib	Sorafenib 400 mg, given orally BID.	
				Placebo → Sorafenib	Sorafenib 400 mg, given orally BID	
SELECT	Phase III, double blind,	• Aged 18 or older. • Measurable, pathologically	• Patients with anaplastic or MTC.	Lenvatinib	Lenvatinib 24 mg (two 10-mg and	DTC including

Schlumberger (2015) Multinational	parallel-group RCT	confirmed DTC. • Evidence of iodine-131–refractory disease. • Received no prior therapy with a TKI or had received one prior treatment regimen with a TKI. • Thyroid-hormone-suppression therapy with TSH levels of ≤ 0.50 mIU/L. • ECOG PS of 0–2. • Adequately controlled BP. • Adequate renal, bone marrow, coagulation, and liver function.	• Any other malignancy within the past 24 months. • Any anticancer treatment 21 days before randomisation. • Significant CV or GI dysfunction.		one 4-mg lenvatinib matched capsules) taken orally QD, continuously.	PTC subpopulation
				Placebo	Matching placebo (two 10-mg and one 4-mg lenvatinib matched capsules) taken orally QD, continuously.	
D4200C00008 Wells (2010) US & France	Phase II, Open-label single-arm study	• Adult patients who had unresectable, locally advanced or metastatic MTC with a confirmed clinical diagnosis of MEN2A, MEN2B, or FMTC and a germline RET mutation were eligible. • The presence of at least one measurable lesion according to RECIST guidelines. • WHO PS of 0 to 2. • Adequate cardiac, hematopoietic, hepatic, and renal function. • Patients with brain metastases were eligible if they were treated with radiation therapy at least 4	• Patients were ineligible if they had received prior chemotherapy and/or radiation therapy within 4 weeks before the initiation of the study therapy. • Patients were excluded if there was evidence of pheochromocytoma based on elevated 24-hour urinary catecholamine levels.	Vandetanib	Once-daily oral doses of Vandetanib 300 mg, until disease progression, unacceptable toxicity, or withdrawal of consent occurred.	MTC and RET mutation

		weeks before entry and were clinically stable without corticosteroid treatment for 1 week.				
D4200C00068 Robinson (2010) Multinational	Phase II, Open-label single-arm study	• Eligible patients had histologically confirmed, unresectable, measurable, locally advanced, or metastatic hereditary MTC with a confirmed diagnosis of MEN2A, MEN2B, or familial MTC by either germline RET mutation or family history. WHO PS of 0–2. • Age ≥18 years. • Adequate cardiac, hematopoietic, hepatic, and renal function. • Brain metastases were permitted if treated at least 4 wk before entry and clinically stable without steroid treatment for 1 wk. • One or more measurable lesions at least 10 mm in the longest diameter by spiral CT scan (5 mm slice thickness) or 20 mm with conventional techniques (>5 mm slice thickness) according to modified RECIST criteria. • Negative PT. • Female subjects must be one year postmenopausal, surgically sterile, or using	• Any anticancer therapy (including surgery, locoregional, biological, immunotherapy, hormonal, or radiotherapy) within 21 days before the first dose of study drug. • Leptomeningeal metastases or brain metastases. • Subjects who have not recovered from toxicities because of prior anticancer therapy. • Significant CV impairment. • Active malignancy (except for adenocarcinoma of the lung or definitively treated melanoma in-situ, BCC or SCC of the skin, or carcinoma in-situ of the cervix) within the past 24months. • Major surgery within 3 weeks before the first dose of study drug. • Bleeding or thrombotic disorders or use of anticoagulants. (Treatment with low molecular weight heparin is allowed.) • Active haemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks	Lenvatinib	24 mg QD in 28-day cycles, until disease progression or unacceptable toxicity	MTC and RET mutation

		an acceptable method of contraception. • Male subjects must be surgically sterile or using an acceptable method of contraception during their participation in this study. • Able to swallow study medication as a whole tablet.	before the first dose of study drug. • Active infection (any infection requiring treatment). • Symptomatic CNS disease. • Subjects having >1+ proteinuria on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria. • Subjects with urine protein greater than or equal to 1 g/24-hour will be ineligible. • Scheduled for surgery during the study.			

EXAM Elisei (2013) Multinational	Phase III, Double-blind, parallel-group RCT	• Histologically confirmed diagnosis of MTC that is unresectable, locally advanced, or metastatic, and disease that is measurable or non-measurable per mRECIST. • At least 18 years old. • ECOG PS ≤ 2. • Documented PD on CT, MRI, bone scan, or X-ray per mRECIST at screening compared with a previous image done within 14 months of screening. • Recovered to NCI CTCAE v3.0 Grade ≤1 from clinically significant AEs due to anti-neoplastic agents, investigational drugs, or other medications that were administered prior to randomisation.	• Received prior systemic anti-tumor therapy within 4 weeks of randomisation. • Received radiation to ≥25% of bone marrow. • Received treatment with other investigational agents within 4 weeks of randomisation • Received treatment with cabozantinib. • Brain metastases or spinal cord compression, unless completed radiation therapy ≥4 weeks prior to randomisation and stable without steroid and without anti-convulsant treatment for ≥10 days. • History of clinically significant hematemesis or a recent history of haemoptysis.	Cabozantinib	140 mg (freebase equivalent) of cabozantinib capsules orally QD, until either intolerable toxicity or disease progression per mRECIST occurred.	MTC and RET mutation

		• Must agree to use medically accepted methods of contraception during the study and for 3 months following discontinuation of study treatments. • No other diagnosis of malignancy and currently has no evidence of malignancy. • Female subjects of childbearing potential must have a negative PT at screening.	• Serious intercurrent illness. • Pregnant or breastfeeding. • The subject has an active infection requiring systemic treatment.	Placebo	140 mg (freebase equivalent) of placebo capsules orally QD, until either intolerable toxicity or disease progression per mRECIST occurred.	
MATiSSe, Ahmed (2011) UK	Phase II, Open-label single-arm study	• Histologically proven, progressive locally advanced/metastatic MTC, or DTC deemed not suitable for treatment with radioactive iodine. • Documented evidence of measurable disease according to the RECIST criteria version 1.0. Age >18 years. • ECOG performance status	• Anaplastic and poorly differentiated carcinoma of the thyroid. • Previous treatment with a TKI or anti-angiogenic agents. • Previous malignancy except cervical cis, BCC or superficial bladder cancer. • Patients with uncontrolled hypertension or those taking 2 or more anti-	Sorafenib	Sorafenib at a dose of 400 mg BID. Dose-level reductions to 400 mg daily and 400 mg alternate days were implemented if patients developed severe toxicity. Drug interruptions were also permitted. Concomitant	MTC and DTC/PTC and RET mutation/fusion

		0 or 1. • One of the following histological sub-types - Any papillary subtypes including follicular variants, tall cell, columnar cell and diffuse sclerosing, - Any follicular, Hürthle cell or medullary. • Lesions which are accessible for low risk biopsy. • Women must be post-menopausal or have a negative PT on entry into the study. • Patients must refrain from becoming pregnant throughout their treatment and for up to 6 months after stopping study drug. • They must be on adequate contraception (abstinence, oral contraceptives, barrier method with spermicide, implantable or injectable contraceptive or surgical sterilisation) throughout this period.	hypertensives. Cranial metastases not radiologically stable over a period of 6 months. • Evidence of active coronary artery disease. Bleeding diatheses. • Concomitant medication with St John's Wort, rifampicin, or warfarin. HIV infection or chronic HBV or HCV. • Patients with CHF NYHA functional class >II. Cardiac arrhythmias greater than Grade 1 NCI CTCAE, Version 3.0. • Patients with Child-Pugh class C hepatic impairment. • Intracranial disease unless there has been radiological evidence of stable intracranial disease > 6 months. In the case of a solitary brain metastasis, evidence of a DFS interval of at least 3 months post-surgery. • All patients previously treated for brain metastases must be stable off corticosteroid therapy for at least 28 days. • Any drug that targets the RAS, VEGF, VEGFR or EGFR pathway. • Significant surgery within 4		bisphosphonates were allowed. Treatment was continued until evidence of radiological progression	

			weeks of start of study. • Investigational drug therapy during or within 30 days. • Any cancer chemotherapy, immunotherapy, RT, or hormonal treatment over the last 4 weeks. Palliative RT to symptomatic disease sites is permitted. • Concurrent anti-cancer chemotherapy, immunotherapy, or hormonal therapy except bisphosphonates. • Women who are pregnant, breast feeding, or planning pregnancy within 6 months after the last treatment. • History of alcohol or substance abuse within the preceding 6 months that may increase the risks associated with study participation or study agent administration or may interfere with interpretation of results. • Recent thromboembolic events including MI. Need for anti-coagulant therapy.			
NCI-2009-00132, Hong (2009) US	Phase I/II, Open-label single arm study	• Age ≥18 years. • Histologically confirmed advanced cancer with ≤4 previous cytotoxic chemotherapies or no standard therapy that could increase survival by	• Continuing grade 3 AEs resulting from therapy administered ≥4 wk earlier • CNS metastases, except patients having previous radiation	Sorafenib + Tipifarnib	A standard 3 + 3 dose-escalation design was used. Each cycle consisted of 28 days of sorafenib and 21 days of	MTC and DTC/PTC and RET mutation/fusion

		3 months. • ECOG PS of ≤2. • RECIST measurable disease on which biopsy can be done, although biopsies were optional. • Women of child-bearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation; should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. • Ability to understand and the willingness to sign a written informed consent document. Tumor accessible for repeat biopsies	• Allergies to imidazoles or compounds similar to sorafenib or tipifarnib • Uncontrolled hypertension • Current bleeding diathesis • ≥ grade 2 peripheral neuropathy • Uncontrolled intercurrent illness • NYHA classification of >2 • Impaired swallowing • Therapeutic anticoagulation • HIV+ • Pregnancy • Childbearing potential individuals unwilling to use adequate contraception		tipifarnib (3 wk on and 1 wk off per 28-d cycle). Level -1: oral sorafenib 400 mg QD + oral tipifarnib 100 mg QD; Level 1: oral sorafenib 400 mg QD + oral tipifarnib 100 mg QD; Level 2: oral sorafenib 400 mg QD + oral tipifarnib 100 mg BID; Level 3 (phase II recommended dose or maximum tolerated dose): oral sorafenib 400 mg every morning and 200 mg every afternoon/evening + oral tipifarnib 100 mg BID; Level 4: oral sorafenib 400 mg every morning and 200 mg every afternoon/evening + oral tipifarnib 200 mg BID; Level 5: oral sorafenib 400 mg every morning and 200 mg every afternoon/evening + oral tipifarnib 300 mg BID; Level 6: oral sorafenib 400 mg BID + oral tipifarnib 100 mg BID. Treatment	

					repeats every 28 days for 12 courses in the absence of disease progression or unacceptable toxicity. Patients may be allowed to continue the treatment after the 12 courses if there is continued clinical response or disease stabilisation, and patients do not have significant toxicities.	
NCI-2009-00196, Lam (2010) US	Phase II, Open-label non-RCT	• Arm A: Histologically confirmed MTC under the clinical setting of inherited tumor syndromes, such as MEN 2A, MEN 2B, or FMTC. • Arm B: Histologically confirmed MTC under the clinical setting of sporadic MTC. • Both arms: • measurable disease. • Metastatic and/or locally advanced or locally recurrent disease. • Oral or IV bisphosphonates therapy will be allowed for patients with bony metastasis at	• Systemic anti-tumor therapy within 4 weeks prior to study entry. • External beam RT within 1 week or if the AEs associated with radiation are not resolved to grade 1 or less prior to study entry. • Prior therapy with sorafenib, ZD 6474 or AMG-706. • Currently receiving any other tumor-specific therapy for thyroid cancer or investigational therapy. • History of allergic reactions attributed to compounds of similar chemical or biologic composition to sorafenib.	Sorafenib	Sorafenib tosylate 400 mg orally BID, on day 1-56, cycle repeated Q8W, until disease progression or unacceptable toxicity	MTC and RET mutation

		the investigator's discretion. • Life expectancy ≥6 months. • ECOG PS 0-2. • Women of child-bearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation, and for at least 30 days after completion of therapy.	• Patients unable to swallow sorafenib tablets. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled hypertension, or psychiatric illness/social situations that would limit compliance with study requirements. • Any evidence of a bleeding diathesis. • Actively receiving anticoagulation with therapeutic intent. • Pregnant women or women who are breast-feeding. • HIV+ patients receiving combination ART because of possible pharmacokinetic interactions with sorafenib (BAY 43-9006). Patients taking the cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine, or phenobarbital), rifampin or St. John's wort due to potential drug interactions with sorafenib.			

XL-184-001, Kurzrock (2011) US	Phase I, Open-label single arm study	• Adult patients with histologically confirmed solid tumours or lymphomas that were metastatic or unresectable who were no longer responding to conventional therapies or who had disease for which no standard therapy exists • ECOG PS score of 0 to 2 • In the MTD expanded cohort: at least 20 subjects with metastatic and/or advanced/locally recurrent MTC not appropriate for surgical resection with measurable disease as defined by RECIST	• Received chemotherapy or immunotherapy within 4 weeks, nitrosourea therapy within 6 weeks, or RT or investigational agents within 30 days of the first dose of cabozantinib. Patients with brain metastases • Uncontrolled intercurrent illness • HIV+ • Administration of an investigational drug within 30 days of the first dose of XL184. Subject has not recovered from AEs due to investigational agents or other medications administered more than 4 weeks before study enrolment • Pregnancy or breastfeeding • Known allergy or hypersensitivity to any of the components of the XL184 formulation.	Cabozantinib	Patients were assigned to 13 dose levels: Dose levels one to nine (0.08, 0.16, 0.32, 0.64, 1.28, 2.56, 5.12, 7.68, and 11.52 mg/kg) explored an intermittent schedule (once daily for 5 days followed by 9 days rest) with a suspension formulation, dose levels 10 to 11 (175 and 265 mg) used continuous fixed daily dosing with a suspension formulation, and dose levels 12 to 13 (175 and 250mg) and the MTD (175mg) cohort used continuous fixed daily dosing with capsules. All patients were instructed to take cabozantinib in a fasting state (2 hours before and 1 hour after administration of cabozantinib).	MTC and RET mutation
				Cabozantinib 0.08-11.52 mg/kg QD		
				Cabozantinib 175-265 mg/kg		
				Cabozantinib 175-250 mg/kg		

					Treatment continued until disease progression or unacceptable AEs.	
ZETA, Wells (2012) Multinational	Phase III, Double-blind, parallel group RCT	• Adults who had measurable, unresectable locally advanced or metastatic, hereditary, or sporadic MTC • Submission of a tumour sample was required except for patients with hereditary MTC who had a documented germline RET mutation • WHO PS of 0 to 2 • Presence of measurable tumour • Able to swallow medication	• Significant cardiac, hematopoietic, hepatic, or renal dysfunction • Administration of chemotherapy and/or RT (with exception of palliative RT) within 4 weeks before random assignment • Major surgery within 4 weeks before randomisation • Brain metastases or spinal cord compression, unless treated at least 4 weeks before first dose and stable without steroid treatment for 10 days • Previous ZD6474 treatment	Vandetanib	Oral vandetanib 300 mg QD, until disease progression	MTC and RET mutation
				Placebo	Oral placebo QD, until disease progression	
09-C-0089, Del Rivero (2019) US	Phase I/II, Open-label non-RCT	• Pathologic confirmation of cancer by the Laboratory of Pathology, NCI. 2 • Phase I: Diagnosis of recurrent, metastatic or primary unresectable solid tumour that does not have curative standard treatment • Phase II: Diagnosis of recurrent, metastatic or	• Patients with cancer potentially curable by surgical excision alone or patients who have not received therapy that might be considered standard • Severe or uncontrolled systemic disease • Untreated brain metastases • During Phase II enrolment:	Vandetanib + Bortezomib	Patients were treated with vandetanib and bortezomib to find the maximally tolerated dose. Daily oral vandetanib and bortezomib on days 1, 4, 8 & 11 every 28 days. Four dose	MTC and RET mutation

		primary unresectable MTC) • Measurable disease at presentation: Either by RECIST or by measurement of serum markers (calcitonin, CEA, PSA or cancer antigen 125 or carbohydrate antigen 125 (CA-125) in the dose-finding portion of the study; with disease measurable by RECIST required only in the phase II cohort • ECOG PS 0 or 1 • Age ≥18 years • Last dose of chemotherapy or experimental therapy more than 4 weeks prior to enrolment date • Any toxicity greater than CTCAE grade 1 from previous anti-cancer therapy must have been resolved • Last RT 4 weeks prior to starting treatment with this protocol except for palliative RT and there must be sites of measurable disease that did not receive radiation • Adequate organ and marrow function • Negative PT • Male patients must be	Prior therapy with vandetanib • Women who are currently pregnant or breast-feeding • The presence of a second malignancy within the last 2 years • Patients with evidence of a bleeding diathesis that cannot be corrected with standard therapy or factor replacement • Any unresolved toxicity greater than CTCAE grade 1 from previous anticancer therapy. Major surgery within 4 weeks, or incompletely healed surgical incision before starting study therapy • Clinically significant CV event • Hypertension not controlled by medical therapy • Currently active diarrhoea greater than or equal to CTCAE Grade 2.0 • Concomitant medications that are potent inducers of cytochrome P450 3A4 function • Major surgery within 4-weeks, or incompletely healed surgical incision before starting study medications		levels were explored, with patients receiving initial doses of bortezomib/vandetanib (mg/m2 B/mg V) of 1/100 (3), 1.3/100 (6), 1.3/200 (6), and 1.3/300 (7).	

		surgically sterile or using an acceptable method of contraception during their participation in this study. Contraceptive use will continue for at least four months after the last dose of study medication	• Inability to take oral medications for whatever reason			
NCT01660984, Kraft (2018) US	Phase I/II, Open-label prospective observational cohort	• Patients 5 to 18 years of age with measurable, locally advanced or metastatic, hereditary MTC • Recovery from toxic effects of prior therapy and adequate performance score and organ function • Patients must have histologically or cytologically confirmed MTC, confirmed by the Laboratory of Pathology, NCI OR Confirmation of MEN2A or MEN2B diagnosis, regardless of presence of MTC • Performance Status: Ability to travel to the NIH and to undergo evaluations to be performed on this protocol • Subjects who have not previously received medical or surgical treatment, patients, who have previously received medical or surgical treatment, and subjects	• In the opinion of the investigator the patient is not able to return for follow-up visits or obtain required follow-up studies.	Vandetanib	Patients received oral vandetanib at two dose levels within the 100–300 mg/m2/day dose range QD, continuously (in 28-day cycles). A standard 3+3 dose escalation design was followed in age groups 13–18 years and 5–12 years. Dose was calculated based on BSA using a dosing nomogram. The recommended phase II dose in the absence of dose limiting toxicity was determined as 100 mg/m2/day. All patients in a subsequent expansion cohort were treated at this dose level.	MTC and RET mutation

		who are currently receiving medical treatment and/or radiation for MEN 2 related manifestation(s) • Inclusion Criteria for Parents or Primary Caregivers: Must be a parent or primary caregiver of a patient (< 21) who has a histologically or cytologically confirmed MTC or who have MEN2 (regardless of MTC status) • Ability to understand and be willing to sign a written informed consent document				

LIBRETTO-001, Wirth (2018) Multinational	Phase I/II, Open-label single arm study	• Phase 1: Patients with a locally advanced or metastatic solid tumour who have progressed on or intolerant to standard therapy or no standard therapy exists, or in the investigator's opinion, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy or decline standard therapy. • Prior MKIs with anti-RET activity, once adequate PK exposure is achieved • Evidence of RET gene alteration in tumour and/or blood required as identified through molecular assays,	• Phase 2 cohorts 1-4: an additional known oncogenic driver • Cohorts 1-5: prior treatment with a selective RET inhibitor • Major surgery within 4 weeks prior to planned start of LOXO-292 • Radiotherapy with a limited field of radiation for palliation within 1 week of planned start of LOXO-292, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose	LOXO-292 - Thyroid	20mg QD -240mg BID in a cycle of 28 days	MTC and RET mutation

		measurable or non-measurable disease determined by RECIST 1.1 or RANO as appropriate to tumour type • ECOG score of 0,1, or 2 or LPS ≥ 40% (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment • Adequate hematologic, hepatic and renal function • Phase 2: The same as phase 1 but with following: For Cohorts 1 and 3 Subjects must have received prior standard therapy appropriate for their tumour type and stage of disease	of study treatment • Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment • Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Patients are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of LOXO-292 and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery [SRS]			

		• Cohorts 1-4: restricted to patients with evidence of a RET gene alteration in tumour. Cohorts 1-4: at least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumour type and not previously irradiated • Cohort 4: radiographic PD within the previous 14 months • Cohorts 1-4 without measurable disease; MTC not meeting the requirements for Cohorts 3 or 4; (a known RET mutation is not required) MTC syndrome spectrum cancers (e.g., MTC,	• Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-292 or prolongation of the QT interval corrected (QTcF) > 470 msec. • Required treatment with certain strong CYP3A4 inhibitors or inducers and certain prohibited concomitant medications	LOXO-292 - All Solid Tumours	20mg QD -240mg BID in a cycle of 28 days	

		pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET alteration/activation were allowed with prior Sponsor approval; cfDNA positive for a RET gene alteration not known to be present in a tumor sample • Cohort 6: Patients who otherwise are eligible for Cohorts 1-5 who discontinued another RET inhibitor due to intolerance were eligible with prior Sponsor approval		LOXO-292 - NSCLC	20mg QD -240mg BID in a cycle of 28 days	

				LOXO-292 - Safety data set over all patients	20mg QD -240mg BID in a cycle of 28 days	

LIBRETTO-321 NCT04280081[6]	Open label/single arm/Phase II	• Adult Chinese patients (≥ 18 years of age) with an advanced tumour harbouring an activating *RET* alteration or a prospectively identified *RET* alteration (fusion or mutation) confirmed by a certified laboratory were eligible for this study • Cohort 1: Patients with advanced *RET* fusion-positive solid tumours who had progressed or were intolerant to one or more prior standard therapies and who had declined, or were considered unsuitable by the investigator for, standard first-line therapy • Cohort 2: Patients with advanced *RET*-mutant MTC regardless of prior systemic therapy (at the time of initiation of this study, there was no approved standard of care for patients with *RET*-mutant MTC in China) • Patients in Cohorts 1 and 2 were also required to have measurable disease as determined by the investigator, evidence of *RET* alteration in the tumour (except in germline DNA for patients with MTC	• Prior therapy with a selective RET inhibitor including investigational agents • Presence of an additional validated oncogenic driver that could cause resistance to selpercatinib (such as targetable BRAF mutations for patients with TC, targetable re-arrangements of ALK in patients with MTC, or activating RAS mutations in patients with TC or MTC) in Cohorts 1 and 2 • Symptomatic primary CNS tumours or metastasis	Selpercatinib	160 mg BID	RET-mutant MTC and RET fusion-positive TC

		in Cohort 2) and have RET status confirmed by central laboratory • Cohort 3: Patients with advanced *RET*-altered solid tumours and patients who did not fulfil the requirements for Cohorts 1 or 2 • Other inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function, and a life expectancy of > 3 months				

Study 308 Zheng (2021)[7]	Double blind/Cross over/RCT/Phase III	• Adult patients ≥ 18 years of age • Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 2 • ≤ 1 prior VEGF/VEGFR-targeted regimen • A histologically or cytologically confirmed diagnosis of RR-DTC with demonstrated evidence of disease progression within 12 months of providing informed consent, as measured by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and confirmed by IIR. • Radioiodine-refractory/resistant disease was defined as having one or more of the following attributes: ○ ≥ 1 measurable lesions with no iodine uptake on radioiodine scan ○ ≥ 1 measurable lesion that has progressed per RECIST v1.1 within 12 months of radioiodine therapy despite	• Please see ClinicalTrials.gov webpage NCT02966093 for full exclusion criteria	Lenvatinib versus placebo	24 mg QD	DTC

		radioiodine avidity at time of treatment, ○ Received cumulative activity of radioiodine of > 600 mCi or 22 gigabecquerels with the last dose administered ≥ 6 months prior to study entry • Patients with specific RR-DTC subtypes were eligible for enrollment: ○ Papillary thyroid cancer (please see ClinicalTrials.gov webpage NCT02966093 for all variants) ○ Follicular thyroid cancer (including Hürthle cell, clear cell, or insular)				

Reddy (2022)[8]	Open label/RCT/Phase II	• Patients with Radioactive Iodine-131 (RAI)-avid advanced metastatic DTC	• Patients with oligometastatic (<5) bone disease and subcentimetric lung nodules	Lenvatinib	Low-dose (10 mg QD)	DTC

VERIFY NCT01876784[9]	Double blind/parallel group/RCT/Phase III	• Provision of informed consent to participate in the study as well as provision of informed consent to provide a sample of a previously obtained archival tumour biopsy • Female or male aged 18 years and older with previously confirmed histological diagnosis of locally advanced or metastatic differentiated (excluding minimally invasive follicular) thyroid cancer not amenable to surgical resection, external beam radiotherapy or local therapy • Measurable disease defined as at least one lesion, not irradiated within 12 weeks of the date of randomisation, that can be accurately measured at baseline • Participants must have experienced progression within 14 months and be RAI-refractory/resistant or unsuitable for RAI • Thyroid-stimulating hormone (TSH) suppression below 0.5 mU/L is required • World Health Organisation	• Inadequate organ function as defined by: ○ (1) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 x upper limit of normal (ULN), or greater than 5.0 x ULN if judged by the Investigator to be related to liver metastases ○ (2) Serum bilirubin greater than 1.5 x ULN. This criterion does not apply to participants with known Gilbert's Disease ○ (3) Creatinine clearance <50 mL/min (calculated by Cockcroft-Gault formula) • Risk of prolonged interval between Q and T (QT) on an electrocardiogram (ECG) corrected for heart rate (QTc) as defined by:	Vandetanib versus placebo	300 mg QD	DTC

		(WHO) or Eastern Cooperative Oncology Group (ECOG) Performance status 0-2 • Negative pregnancy test (urine or serum) for female participants of childbearing potential	○ (1) Current therapy with any medication known to be associated with Torsades de pointes or potent inducers of cytochrome CYP3A4 ○ (2) History of QT prolongation ○ (3) Congenital long QT syndrome ○ (4) QT interval corrected for heart rate by the Bazett's method (QTcB) correction unmeasurable or greater than 480 ms on screening ECG • Previous therapy with approved or investigational tyrosine kinase or anti-VEGF receptor inhibitors or targeted therapies (e.g. multi-targeted kinase inhibitors such as sorafenib, AMG-706, sunitinib, pazopanib, lenvatinib) • RAI therapy within 12 weeks prior to first dose of study drug, and radiation therapy other than RAI, including external beam, if not completed prior to			

			randomisation			

NCT02143726[10]	Open label/Crossover/RCT/Phase II	• Patients must have 10 representative hematoxylin and eosin (H&E) stained thyroid tissue slides OR tumor block available for submission to central pathology review. This review is mandatory prior to registration to confirm eligibility • Patients must have measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST) criteria, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral computed tomography (CT) scan. CT must be performed within 28 days of registration. • Radioactive iodine (RAI) - refractory disease defined as 1 or more of the following: ○ Patients who have received greater than 600 mCi of radioactive iodine in their lifetime OR	• No history of major surgery ≤ 28 days of registration • No history of intracranial brain metastasis • Cardiovascular disease. No history of any of the following ≤ 6 months of registration: • Myocardial infarction or unstable angina • New York Heart Association grade III or greater congestive heart failure • Cerebrovascular accident • Grade 3 or 4 peripheral ischemia • Grade 3 or 4 thromboembolic event • Liver disease: No history of the following: • Child Pugh Class B or C liver disease • "Chronic active" hepatitis defined as: • 1) Hepatitis B surface antigen (HBsAg) > 6 months • 2) Serum hepatitis B virus (HBV) deoxyribonucleic acid (DNA) 20,000 IU/ml (105 copies/ml), lower values 2,000-20,000 IU/ml (104-105 copies/ml) are often seen in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B	Sorafenib versus Sorafenib plus everolimus	Sorafenib: 400 mg BID; everolimus: 5 mg QD	DTC

		○ RAI-avid metastatic lesion which remained stable in size or progressed despite RAI treatment within 9 months of RAI treatment OR ○ 10% or more increase in serum thyroglobulin (on thyroid-stimulating hormone [TSH]-suppression) within 9 months of RAI treatment OR ○ Index metastatic lesion non-RAI avid on a diagnostic RAI scan OR ○ Presence of fluorodeoxyglucose (FDG) avid metastatic lesions on positron emission tomography (PET)/CT scan (standardized uptake values	• 3) Persistent or intermittent elevation in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels • 4) Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation • No history of gastrointestinal fistula or gastrointestinal perforation < 90 days of registration • No known history of prolonged QT syndrome • No Grade 3 or 4 hypertension (systolic blood pressure [BP] >160 and or diastolic BP > 100) that cannot be controlled with medication prior to registration • Concomitant medications: • Chronic concomitant treatment with strong inhibitors of cytochrome P450 3A4 (CYP3A4) is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. • Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must			

		[SUV]max > 5 of any single lesion)
		• Progressive disease defined by RECIST criteria ≤ 14 months
		• Patients must have metastatic disease or locally advanced unresectable disease
		• Prior treatment:
		  ○ Patients may have received prior radiation therapy to index lesions ≥ 28 days prior to registration on this protocol if there has been documented progression by RECIST criteria. Prior radiation therapy to the non-index lesions is allowed if ≥ 28 days prior to registration on this protocol.
		  ○ Prior RAI therapy is allowed if ≥ 90 days prior to registration on this protocol and evidence of
			discontinue the drug 14 days prior to the start of study treatment.
			• Patients requiring anticoagulation must be on stable dose of medication prior to registration.
			• Not pregnant and not nursing, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown. Therefore, for women of childbearing potential only, a negative serum pregnancy test done ≤ 7 days prior to registration is required
			•			

		progression (as defined above) has been documented in the interim (a diagnostic study using < 10 mCi of RAI is not considered RAI therapy). ○ Prior chemotherapy is allowed if ≥ 28 days prior to registration on this protocol ○ Patient may have received any number of prior lines of therapy. ○ No prior use of sorafenib or an mammalian target of rapamycin (mTOR) (including phosphoinositide 3-kinase [PI3k] or protein kinase B [AKT]) inhibitor for the treatment of thyroid cancer • Age ≥ 18 years • Eastern Cooperative				

		Oncology Group (ECOG) Performance Status ≤ 2
		• Required Initial Laboratory Values:
		  ○ Absolute neutrophil count (ANC) ≥ 1,500/mm^3
		  ○ Platelet count ≥ 100,000/mm^3
		  ○ Creatinine ≤ 1.5 mg/dL OR
		  ○ Calculated creatinine clearance ≥ 30 mL/min
		  ○ Total bilirubin ≤ 1.5 x upper limits of normal (ULN)
		  ○ Serum glutamic oxaloacetic transaminase (SGOT) (AST) ≤ 2.5 x ULN
		  ○ Fasting serum cholesterol ≤ 300 mg/dL
		• Documentation of disease: Histologic Documentation - Eligible patients must have histopathologically confirmed Hürthle cell thyroid cancer by central review				

NCT02702388 Brose (2022)[11]	Open label/single arm/Phase I/II	• Patients ≥18 years of age • ECOG PS of ≤2 • 1 or no prior vascular endothelial growth factor (VEGF)/VEGF receptor–targeted therapy • Adequate organ function • A histologically or cytologically confirmed diagnosis of RR-DTC, with both evidence of disease progression within 13 months before providing informed consent and measurable disease assessed by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) confirmed by central radiographic review	• A complete list of the exclusion criteria can be found in the trial listing on www.clinicaltrials.gov (NCT02702388).	Sorafenib plus tipifarnib	Each cycle consisted of 28 days of sorafenib and 21 days of tipifarnib (three weeks on and one week off per 28-day cycle)	MTC and DTC/PTC and RET mutation/fusion

Abbreviations: ALT: alanine aminotransferase; AST: Aspartate aminotransferase; BID: twice daily; CNS: central nervous system; RCT: randomised controlled trial; MTC: medullary thyroid cancer; PTC: papillary thyroid cancer; DTC: differentiated thyroid cancer; PT: pregnancy test; RECIST: response evaluation criteria in solid tumours; TSH: thyroid-stimulating hormone; RAI131: radioiodine therapy; CTCAE: common terminology criteria for adverse events; LFT's: liver function tests; FDG uptake: fluorodeoxyglucose uptake; ECOG PS: eastern oncology group performance status; TKI's: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; BP: blood pressure; GI: gastrointestinal

Appendix C: R code and estimates of shape and scale parameters for the stratified and independent Weibull distributions

The R code used to model the stratified and independent Weibull distributions and fit is provided below, along with estimates of shape and scale parameters provided in Table 2.

```
#Simulate data first
set.seed(1)
n= 200
final.data = data.frame(ID=1:n,time=rexp(n),Event=rbinom(n,1,0.6),Treatment=sample(size=n,c("A","B"),replace=TRUE))
final.data$Treatment <- factor(final.data$Treatment)
final.data$Treatment <- relevel(final.data$Treatment, ref = "B")

#Fit stratified Weibull model
library(survminer)
library(flexsurv)
model1 <- as.formula(Surv(time, Event ) ~ Treatment)
weibl1 <- flexsurvreg(model1,data=final.data, dist="weibull",anc = list(shape = ~ Treatment))

#Now fit independent model
model3 <- as.formula(Surv(time, Event ) ~ 1)
weibl3 <- flexsurvreg(model2,data=final.data[final.data$Treatment=="B",], dist="weibull")
```

Table 2: Estimates of shape and scale parameters from the stratified and independent Weibull model

Model	Shape	Scale	TreatmentA	Shape (TreatmentA)
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Independent Weibull	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A: not applicable.

References

1. NHS England. National Cancer Drugs Fund list. Updated 24th June 2024. Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. [Last accessed]: 26th June 2024.
2. National Institute for Health and Care Excellence. TA742: Selpercatinib for treating advanced thyroid cancer with RET alterations. Available from: https://www.nice.org.uk/guidance/ta742. [Last accessed: 25th April 2023].
3. Eli Lilly and Company. Data on File. LIBRETTO-001 CSR (13th January 2023 data cut-off).
4. National Institute for Health and Care Excellence. TA535: Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta535 [Last accessed: 25th April 2023].
5. Wells Jr SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. Journal of clinical oncology 2012;30:134.
6. 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. Ther Adv Med Oncol 2022;14:17588359221119318.
7. Zheng X, Xu Z, Ji Q, et al. A Randomized, Phase III Study of Lenvatinib in Chinese Patients with Radioiodine-Refractory Differentiated Thyroid Cancer. Clin Cancer Res 2021;27:5502-5509.
8. Singareddy CTR, Satapathy S, Ballal S, et al. Efficacy of radioiodine therapy plus low dose lenvatinib in advanced metastatic differentiated thyroid cancer: A randomised controlled trial. Journal of Nuclear Medicine 2023;64(Suppl 1):254.
9. ClinicalTrials.gov. NCT01876784. Evaluation of Efficacy, Safety of Vandetanib in Patients With Differentiated Thyroid Cancer (VERIFY). Available from: https://clinicaltrials.gov/study/NCT01876784. [Last accessed: 26th June 2024].
10. ClinicalTrials.gov. NCT02143726. Sorafenib Tosylate With or Without Everolimus in Treating Patients With Advanced, Radioactive Iodine Refractory Hurthle Cell Thyroid Cancer. Available from: https://clinicaltrials.gov/study/NCT02143726. [Last accessed: 26th June 2024].
11. Brose MS, Panaseykin Y, Konda B, et al. A Randomized Study of Lenvatinib 18 mg vs 24 mg in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer. J Clin Endocrinol Metab 2022;107:776-787.