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

Confidential information redacted

Highly specialised technologies evaluation committee, 10 April 2024

Chair: Paul Arundel

Lead team: Tina Garvey, Iolo Doull, Ed Wilson

External assessment group: Liverpool Reviews and Implementation Group

Technical team: Kirsty Pitt, Christian Griffiths, Jasdeep Hayre

Company: Lilly

Selpercatinib for untreated advanced thyroid cancer with *RET* alterations

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on thyroid cancer

Rare cancer with potential genetic variations

Epidemiology

- Accounts for around 1% of all new cancer cases in the UK
- Incidence higher in females (72% in UK)

Diagnosis and classification

- Symptoms include lumps and pain in the neck, hoarseness and coughing, and in MTC, dysregulation of calcitonin signalling can lead to severe diarrhoea, Cushing syndrome, bone pain, fatigue and weight loss
- Can arise in the follicular or non-follicular cells
    - 5 subtypes of follicular – can be differentiated or undifferentiated - but subsequently referred to collectively as 'TC'
    - Non-follicular: medullary thyroid cancer (MTC) accounts for ~4% of all thyroid cancer cases

RET alterations

- Activation of *RET* oncogene occurs via *RET* fusions (mostly in TC) and *RET* point mutations (more common in MTC)
- *RET* mutations in MTC are likely associated with a poorer prognosis but no consensus on whether *RET*-fusion positive TC is associated with a worse prognosis

Patient perspectives

Selpercatinib offers potential to delay progression and reduce side effects

Submissions from British Thyroid Foundation, Butterfly Thyroid Cancer Trust, AMEND

- Symptoms such as fatigue and diarrhoea have huge impact on quality of life, even preventing people from leaving the house
- Most patients will no longer be able to work or go to school and are likely to be isolated socially - psychological impact can be substantial
- Currently available treatments often cause significant side effects, including hypertension, hand and foot skin reactions, fatigue, constipation, diarrhoea, nausea and vomiting
- Availability of selpercatinib offers potential for symptoms to reduce allowing people to increase level of activity, and also to experience fewer side effects than with current treatment
- Selpercatinib is an oral formulation so accessible for most patient groups

MTC significantly affected my daily life before treatment. I was in a lot of pain, with fatigue, and had unmanageable diarrhoea that left me unable to leave home and impacted on my ability to work

This drug is the best thing that's happened to me since I was diagnosed with cancer…I definitely have more energy and some days I don't even think about the fact that I have cancer

Abbreviations: MTC, medullary thyroid cancer

Clinical perspectives

Selpercatinib associated with less toxicity than current standard treatments

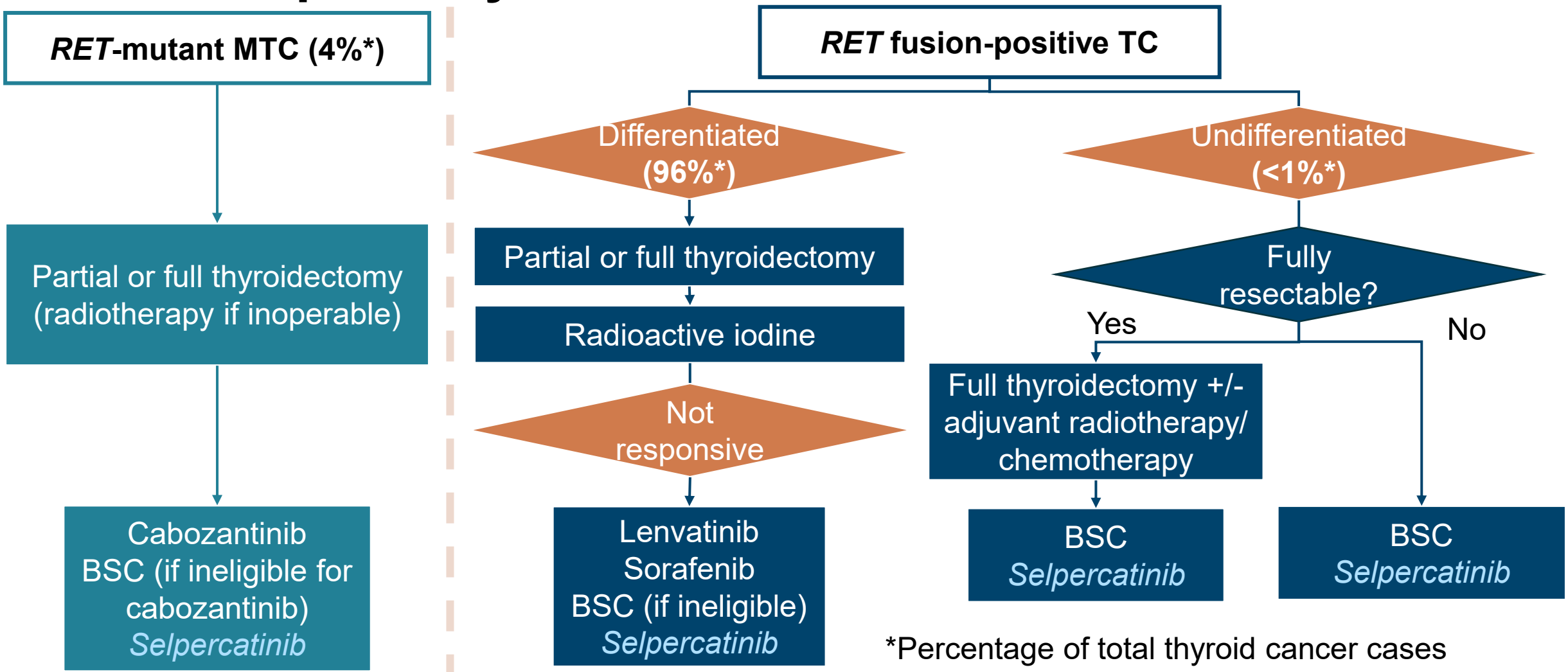
- Unmet need
    - Existing treatments not proven to extend survival and associated with significant side effects, which can impair quality of life
    - No existing treatment for people under 18
- Selpercatinib is so much better tolerated than current treatments that patients are able to continue usual daily activities, often including returning to work. This is very unlikely with current treatments because of side effects
    - Anticipated that people would require less frequent hospital visits for monitoring with selpercatinib, and fewer supportive medicines to manage side effects
- Molecular genetic testing for RET alterations is well established in UK

Equality considerations

- Females are more likely to be diagnosed with thyroid cancer (72%)
- Patient organisation stated that children with MTC should have access to selpercatinib
- There is unequal access to treatments across the country e.g. regional variation in molecular testing practices, however the transition to testing at Genomic Hubs in England should standardise this

Abbreviations: MTD, medullary thyroid cancer

Treatment pathway



*Percentage of total thyroid cancer cases

Company and EAG:
cabozantinib main comparator
~ 10% would have BSC

Company and EAG: <5% have sorafenib so not a main comparator

What are the appropriate comparators for selpercatinib?

Abbreviations: BSC, best supportive care

Selpercatinib (Retsevmo, Lilly)*

*Link to Decision problem

Marketing authorisation	*RET*-mutant MTC • MHRA conditional MA granted February 2023: • Patients aged ≥12 years with advanced *RET*-mutant MTC *RET* fusion-positive TC • EU MA granted March 2024: • Adults and adolescents 12 years and older with advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)
Mechanism of action	Selective kinase inhibitor, targeting the *RET* tyrosine kinase receptor
Administration	Oral capsules
Price	List price: • 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 A PAS is in place

EAG comments: evidence for patients aged 12-18y is limited (n=[redacted]) for *RET*-mutant MTC in LIBRETTO-001, none for *RET* fusion-positive TC) but clinical advice that trial data is generalisable to this group.

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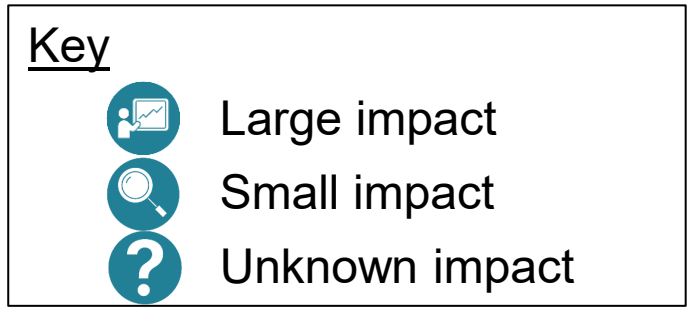
Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; MHRA, Medicines and Healthcare products Regulatory Agency; MA, marketing authorisation; PAS, patient access scheme

Key issues



Issue	ICER impact
Selpercatinib overall survival – RET-mutant MTC	Large
Cabozantinib overall survival – RET-mutant MTC	Large
Selpercatinib overall survival – RET fusion-positive TC	Large
Dose adjustments	Unknown
Utilities	Large in RET-mutant MTC, Small in RET fusion-positive TC
Severity weighting	Large
Other areas of uncertainty: • Clinical effectiveness evidence limitations • RET-mutant MTC population – limitations of MAIC • RET fusion-positive TC population – limitations of naïve unadjusted ITC • Selpercatinib safety evidence	Unknown

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; MAIC, matched-adjusted indirect comparison; ITC, indirect comparison

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Key clinical trials

LIBRETTO-531 has shorter follow-up than LIBRETTO-001

Clinical trial designs and outcomes

	LIBRETTO-001 (n=837)	LIBRETTO-531 (n=291)
Design	Phase 1/2	Phase 3
Date	Started May 17, latest data cut off Jan 23	Started Feb 20, latest data cut off May 23
Population	Patients with locally advanced or metastatic solid tumours (including with *RET* alterations), aged ≥18 years (aged ≥12 years where permitted by local regulatory authorities) who previously had, could not have standard therapy, or no standard therapy exists	Patients aged ≥18 years (aged ≥12 years where permitted by local regulatory authorities) with locally advanced or metastatic MTC with a *RET* alteration (somatic or germline) and no previous treatment with kinase inhibitors
Comparator(s)	None	Cabozantinib or vandetanib (physician's choice, but only cabozantinib since Nov 2021)
Locations	16 countries incl. UK	21 countries incl. UK
Used in model?	Yes	No

Abbreviations: MTC, medullary thyroid cancer

RET-mutant MTC: indirect treatment comparison – methods*

Company's unanchored MAIC with cabozantinib and BSC

LIBRETTO-001

- Effective sample size after weighting = 157

Weighted any-line *RET*-mutant MTC population curve

Matched with

PFS

OS

EXAM trial (Locally advanced/metastatic MTC)

- Clinical effectiveness results only reported for any-line population - 21.5% received prior MKI/TKI therapy

Unweighted *RET*-mutant MTC cabozantinib (n=107) /placebo (n=62, proxy for BSC) arm curves

Unweighted *RET* M918T mutation-positive cabozantinib (n=81) /placebo arm (n=45) curves

EAG comments

- Many of the prognostic factors and effect modifiers that company identified as important were not reported in either trial so could not be adjusted for – potential bias (but unknown which way)
- Using EXAM placebo arm as proxy for BSC is reasonable for PFS but not for OS as 49.5% subsequently received systemic therapies
- Results using LIBRETTO-001 cabozantinib/vandetanib-naïve population would be informative (as all EXAM patients were cabozantinib-naïve)
- LIBRETTO-531 results likely to be most relevant for *RET*-mutant MTC
- Overall, reported effect estimates may not be true treatment effect but broad conclusions are likely valid

Abbreviations: MTC, medullary thyroid cancer; BSC, best supportive care; MAIC, matched-adjusted indirect treatment comparison; PFS, progression-free survival; OS, overall survival

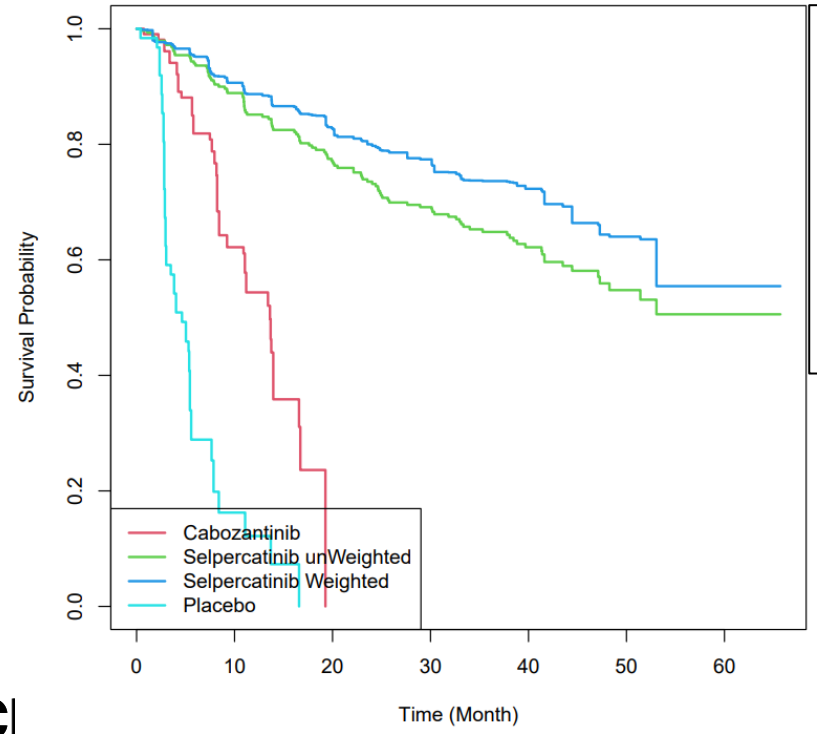
*Link to ITC: baseline characteristics, RET-mutant MTC

RET-mutant MTC: indirect treatment comparison - results

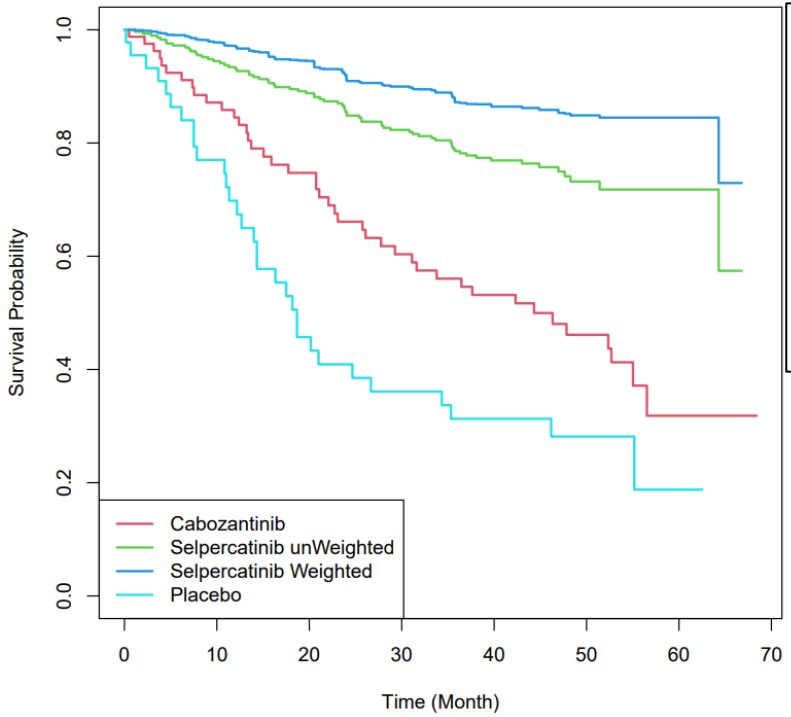
Results suggest selpercatinib improves PFS and OS

	PFS HR (95% CI)	OS HR (95% CI)
Selpercatinib versus cabozantinib		
Unadjusted indirect comparison	0.12 (0.09 to 0.17)	0.38 (0.26 to 0.56)
MAIC	0.08 (0.05 to 0.13)	0.20 (0.13 to 0.32)
Selpercatinib versus BSC		
Unadjusted indirect comparison	0.07 (0.04 to 0.10)	0.21 (0.14 to 0.32)
MAIC	0.05 (0.03 to 0.09)	0.11 (0.07 to 0.18)

NB. All P values <0.001



PFS for selpercatinib vs cabozantinib and placebo before and after weighting



OS for selpercatinib vs cabozantinib and placebo before and after weighting

Abbreviations: BSC, best supportive care; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence intervals; MAIC, matched-adjusted indirect comparison

RET fusion-positive TC: ITC - methods*

Company's naïve, unadjusted indirect comparisons with lenvatinib, sorafenib and BSC

Company

- Company compared individual patient-level data from LIBRETTO-001 any-line population to digitised SELECT and DECISION KM curves to compare selpercatinib with lenvatinib, sorafenib and BSC (used placebo arms as a proxy for BSC)

	SELECT	DECISION
Treatment arms	Lenvatinib vs placebo	Sorafenib vs placebo
Population	Radioactive iodine-refractory differentiated or poorly-differentiated thyroid cancer (no *RET* status reported)	Radioactive iodine-refractory differentiated or poorly-differentiated thyroid cancer (no *RET* status reported)
Prior treatment	0 or 1 prior TKI/MKI - OS data not reported separately for number of prior treatments so company included any-line population in ITC	No prior targeted therapy
Post-progression treatment crossover	87.8% placebo arm crossed over to receive lenvatinib - company adjusted KM OS curves for crossover	71.4% placebo arm crossed over to receive sorafenib - not possible to adjust for crossover due to availability of data so company didn't use DECISION placebo arm for OS

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; ITC, indirect treatment comparison; TKI, tyrosine kinase inhibitor; MKI, multikinase inhibitor; OS, overall survival

*Link to ITC: baseline characteristics, RET fusion-positive TC

RET fusion-positive TC: ITC - results

High uncertainty in ITC means relative efficacy of selpercatinib is unclear

Treatment comparison	PFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
LIBRETTO-001 vs SELECT				
Selpercatinib vs lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
LIBRETTO-001 vs DECISION				
Selpercatinib vs sorafenib	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib vs BSC	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Unadjusted indirect comparison was only method that could have been used but is highly susceptible to bias – not accounting for differences in trial or patient characteristics
- OS data unavailable for systemic-naïve population in SELECT but was available for PFS and could have been compared with systemic-naïve population of LIBRETTO-001 (small population)
- Systemic-naïve LIBRETTO-001 population could also have been used to compare to DECISION for PFS and OS
- Fundamental differences between the LIBRETTO-001, SELECT and DECISION trial populations
  - e.g. number of prior TKIs, median time from diagnosis, RET fusion status unknown in SELECT & DECISION, ECOG status generally poorer in LIBRETTO-001
- Clinical advice to EAG that SELECT and DECISION placebo arms not good proxies for BSC OS data, largely because of subsequent treatments
- For selpercatinib vs BSC, proportional hazards assumption appears violated for PFS and OS. EAG also considers violated for selpercatinib vs sorafenib in OS

Abbreviations: BSC, best supportive care; PFS, progression-free survival; OS, overall survival

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Company's model

Partitioned survival model

Model structure

- Cohort-based partitioned survival model with 3 mutually exclusive health states:
  - Progression-free
  - Progressed disease
  - Death
- Cycle length is one week
- Time horizon 35 years

Assumptions with greatest effect on ICER

- Selpercatinib OS estimates
- Distribution used to generate OS estimates for patients treated with cabozantinib (*RET*-mutant MTC vs cabozantinib)
- Utility values (*RET*-mutant MTC vs cabozantinib and *RET* fusion-positive TC vs lenvatinib)

Abbreviations: OS, overall survival; MTC, medullary thyroid cancer; TC, follicular thyroid cancer

Key Issue: Selpercatinib overall survival (*RET*-mutant MTC)*

Adjustment factor applied to Weibull distribution to align with clinical plausibility

Company

- Fitted 19 parametric distributions to selpercatinib OS MAIC weighted curve
- Clinical expert opinion was elicited on proportions of patients anticipated to be alive at different timepoints following each treatment, and stratified Weibull extrapolation selected for selpercatinib

EAG comments

- In original company base case, OS estimates from Weibull extrapolation were higher than the clinical expert estimates
  - In response to clarification, company applied an adjustment factor of 2 at 5 years to make 10- and 20- survival estimates align more with clinical expert estimates
- EAG has explored different adjustment factors

Distribution	10-year survival	20-year survival
Clinical experts' most likely value	[redacted]	[redacted]
Clinical experts' plausible range	[redacted]	[redacted]
Stratified Weibull (no adjustment)	[redacted]	[redacted]
Revised company base case (adjustment factor of 2): stratified Weibull	[redacted]	[redacted]
EAG pessimistic OS extrapolation (adjustment factor of 3.5 applied at 5y)	[redacted]	[redacted]
EAG optimistic OS extrapolation (adjustment factor of 1.5 applied at 5y)	[redacted]	[redacted]

Which adjustment factor is most plausible to use for selpercatinib OS?

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Abbreviations: OS, overall survival; MAIC, matched-adjusted indirect comparison

*Link to OS extrapolations graph

Key Issue: Cabozantinib overall survival (*RET*-mutant MTC)

Company applies HR from EXAM to BSC Weibull distribution

Company

- To generate OS estimate for BSC: used stratified Weibull distribution from the EXAM placebo arm data (RET M918T-positive population)
- To generate OS estimate for cabozantinib: applied hazard ratio (HR) from EXAM RET-mutant MTC population to the BSC extrapolation

EAG comments

- In company base case (revised at clarification), 20-year OS estimates for cabozantinib were slightly lower than clinical expert estimates of the most likely value
- EAG prefers to apply the HR to the BSC stratified spline 1 knot distribution, to generate a 10-year OS estimate closer to the most likely values range suggested by clinical experts

Distribution	10-year survival	20-year survival
Clinical experts' most likely value	[redacted]	[redacted]
Clinical experts' plausible range		
Revised company base case: stratified Weibull	[redacted]	[redacted]
EAG preferred: stratified spline 1 knot	[redacted]	[redacted]

Which distribution is most plausible for cabozantinib OS in *RET*-mutant MTC?

Abbreviations: OS, overall survival; HR, hazard ratio; BSC, best supportive care

*Link to OS extrapolations graph

Key Issue: Selpercatinib overall survival (*RET* fusion-positive TC)*

Company uses piecewise exponential distribution with adjustment factor

Company

- Fitted 20 parametric distributions to LIBRETTO-001 selpercatinib OS data (any-line *RET* fusion-positive)
- Piecewise exponential distribution chosen to align with clinical expert estimates
- Applied a 1.2 adjustment factor at 5y after clarification to be consistent with approach in *RET*-mutant MTC

EAG comments

- Adjustment factor gives OS estimates that do not fit KM data well after 18 months
- Implemented 2 alternative approaches (see table)
- Note OS estimates for all treatments highly uncertain as use results from naive, unadjusted indirect comparisons

Distribution	10-year survival	20-year survival
Clinical experts' most likely value	[redacted]	[redacted]
Clinical experts' plausible range	[redacted]	[redacted]
Revised company base case: piecewise exponential with adjustment factor of 1.2 at 5y	[redacted]	[redacted]
EAG pessimistic OS extrapolation (adjustment factor of 1.5 applied from 18 months)	[redacted]	[redacted]
EAG optimistic OS extrapolation (adjustment factor of 0.9 applied from 60 months)	[redacted]	[redacted]

Which adjustment factor is most plausible to use for selpercatinib OS in *RET*-mutant MTC?

Abbreviations: OS, overall survival; MAIC, matched-adjusted indirect comparison; KM, Kaplan-Meier

OS extrapolations: *RET* fusion-positive TC

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Abbreviations: KM, Kaplan-Meier; BSC, best supportive care

Key issue: Dose adjustments

EAG consider adherence data should be used instead of RDI multiplier

Background

- Relative dose intensity (RDI) is the average amount of planned dose that a person had
- Adherence is the proportion of days on which people had treatment

Company

To reflect dose reductions due to treatment toxicity, company used an RDI multiplier

- Assumed patients having cabozantinib or lenvatinib received the recommended dose for first 4 model cycles, then a mean RDI multiplier used from cycle 5

EAG comments

Cabozantinib and lenvatinib have a flat price for all recommended doses, therefore costs should have been adjusted for dose adherence

- Adherence data preferred by committee in TA928 – because costs of cabozantinib will depend on the proportion of survival time in which patients receive treatment, rather than the average dose received
- Adherence data may become available from LIBRETTO-531 – data currently suggest that proportion of patients with at least 1 dose interruption is substantially higher for patients having cabozantinib (81.9%) than for patients having selpercatinib (56.0%)
- Has provided scenario where RDI is removed to assume no cost savings from missed/interrupted doses

Should RDI multiplier or adherence data be used to calculate dose adjustments?

Abbreviations: RDI, relative dose intensity

Key issue: Utilities

Company uses utility values from vignette study

Background

- Utility values from a vignette study by Fordham et al. (2015) accepted in TA742 and TA516
  - Committees highlighted concerns that EQ-5D methods would usually be preferred by NICE to inform utility values as they are more robust

Company used Fordham 2015 utility values

EAG comments

- Progression-free health state utility value of 0.8 seems high and close to general population values. When age- and sex-matched to the *RET*-mutant MTC population, general population utility value is 0.845. When matched to *RET* fusion-positive TC population, general population utility is 0.857.
- Progressed-disease health state utility value appears low (0.5)
- Agree with company that utility values generating from mapping any-line *RET*-mutant MTC population data from LIBRETTO-001 are not plausible as progressed disease values are higher than progression-free values
- However, prefer to use values mapped from *RET* fusion-positive TC population data from LIBRETTO-001

Health state	Mean health state utility value	
	Company	EAG preferred
Progression-free	0.80	[redacted]
Progressed disease	0.50	[redacted]

- EAG acknowledges small numbers of patients ([redacted] for progression-free, [redacted] for progressed disease)

Are utility values from Fordham 2015 or mapped from LIBRETTO-001 more plausible?

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer

Key issue: QALY weightings for severity*

Background

- EAG and company agree that severity weighting applies for **company base case** comparisons with cabozantinib and BSC
- EAG doesn't apply severity modifier to cabozantinib comparison in **some** scenarios
  - Including EAG scenario 1 or 2 increases the total QALYs for people having cabozantinib (decreasing QALY shortfall) so severity modifier is not included for comparisons with cabozantinib that include either of these amendments
  - EAG does **not** apply severity modifier in **EAG base case** for comparison with cabozantinib

Company base case	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	Absolute QALY shortfall (has to be >12)	Proportional QALY shortfall (has to be >0.85)	Severity modifier applied
RET-mutant MTC	14.34	Cabozantinib: 2.11 BSC: 1.52	12.23 12.82	0.8529 0.8940	1.2 1.2
RET fusion-positive TC	13.38	Lenvatinib: 2.62 BSC: 1.27	10.76 12.11	0.8035 0.9044	1 1.2

In which comparisons and scenarios is it appropriate to apply a severity modifier?

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Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year

*QALY weightings for severity - background

Summary of company and EAG base case assumptions

EAG prefers some alternate extrapolations for OS and alternate utility values

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Selpercatinib OS	***RET*-mutant MTC** Stratified Weibull with adjustment factor of 2 ***RET* fusion-positive TC** Piecewise exponential distribution with adjustment factor of 1.2	***RET*-mutant MTC** Stratified Weibull with adjustment factor of 2 Scenario analyses: - adjustment factor of 3.5 applied at 5y - adjustment factor of 1.5 applied at 5y ***RET* fusion-positive TC** Piecewise exponential distribution with adjustment factor of 1.2 Scenario analyses: - adjustment factor of 1.5 applied at 18 months - adjustment factor of 0.9 applied at 60 months
Cabozantinib OS	Applied HR from EXAM to BSC Weibull distribution	Applied HR from EXAM to BSC stratified spline 1 knot distribution
Utility values	Fordham 2015 utility values	Values mapped from *RET* fusion-positive TC population data from LIBRETTO-001

Abbreviations: MTC, medullary thyroid cancer; HR, hazard ratio; BSC, best supportive care

Cost-effectiveness results

- Some ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- Fully incremental analyses (where treatment options are ranked by ascending cost) are presented in PART 2 slides, because of confidential comparator discounts
- All ICERs presented include PAS discount for selpercatinib

Company base case results – RET-mutant MTC, pairwise

Deterministic incremental base case results, pairwise: selpercatinib vs comparator

Technology	Total costs	Total QALYs	ICER with 1.2 severity modifier (£/QALY)
Selpercatinib	[redacted]	[redacted]	-
Cabozantinib	Confidential	2.08	>£30,000
Best supportive care	£17,089	1.51	£39,481

Probabilistic incremental base case results, pairwise: selpercatinib vs comparator

Technology	Total costs	Total QALYs	ICER with 1.2 severity modifier (£/QALY)
Selpercatinib	[redacted]	[redacted]	-
Cabozantinib	Confidential	2.11	>£30,000
Best supportive care	£17,110	1.52	£39,458

Results include PAS for selpercatinib but do not include confidential commercial discounts for comparators

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Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

EAG deterministic scenario analyses – *RET*-mutant MTC

All ICERs >£30,000. Selpercatinib OS extrapolation has greatest impact on ICER

No.	Scenario (applied to above base case)	ICER (£/QALY) vs cabozantinib	ICER incl 1.2x modifier (£/QALY) vs BSC
	Company base case	>£30,000*	£39,481*
1	Mapped utility values from LIBRETTO-001 *RET* fusion-positive TC population	23.7% increase	£39,689*
2	Stratified spline 1 knot distribution to extrapolate cabozantinib OS	18.8% increase	N/A
1+2	**EAG base case**	>£30,000	**£39,689***
1+2, 3a	Selpercatinib OS: adjustment factor of 3.5 at 5y	36.3% increase	£51,150*
1+2, 3b	Selpercatinib OS: adjustment factor of 1.5 at 5y	13.3% decrease	£35,141*

*Includes severity modifier of x1.2

- Including EAG scenario 1 or 2 increases the total QALYs for people having cabozantinib so severity modifier is not included for comparisons with cabozantinib that include either of these amendments

Results include PAS for selpercatinib but do not include confidential commercial discounts for comparators

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year

Company base case results – *RET* fusion-positive TC

Deterministic incremental base case results, pairwise: selpercatinib vs comparator

Technology	Total costs	Total QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	-
Lenvatinib	Confidential	2.62	>£30,000
BSC	16,030	1.27	£37,050*

Probabilistic incremental base case results, pairwise: selpercatinib vs comparator

Technology	Total costs	Total QALYs	ICER (£/QALY)
Selpercatinib	[redacted]	[redacted]	-
Lenvatinib	Confidential	2.63	>£30,000
BSC	15,983	1.28	£37,025*

*Severity modifier of 1.2x applied to incremental QALYs and ICERs for selpercatinib vs BSC

Results include PAS for selpercatinib but do not include confidential commercial discounts for comparators

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; BSC, best supportive care

EAG deterministic scenario analyses – RET fusion-positive TC

EAG scenario analyses (deterministic)

No.	Scenario (applied to above base case)	ICER (£/QALY) vs lenvatinib	ICER incl 1.2x modifier (£/QALY) vs BSC
	Company base case	**>£30,000**	**£37,050**
1	Mapped utility values from LIBRETTO-001 RET fusion-positive TC population	3.3% decrease	£36,312
1	**EAG base case**	**>£30,000**	**£36,312**
1, 2a	Selpercatinib OS: adjustment factor 1.5 at 18 months	43.3% increase	£45,285
1, 2b	Selpercatinib OS: adjustment factor of 0.9 at 60 months	15.7% decrease	£32,368

Results include PAS for selpercatinib but do not include confidential commercial discounts for comparators

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

The company has not submitted a managed access proposal but the following evidence could be considered if necessary

- For LIBRETTO-001, [redacted]
- LIBRETTO-531 is ongoing in MTC only. Median follow-up at last data cut in May 2023 was 12 months.

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- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Issue	ICER impact	Slide
Selpercatinib overall survival – RET-mutant MTC	Large	18
Cabozantinib overall survival – RET-mutant MTC	Large	19
Selpercatinib overall survival – RET fusion-positive TC	Large	20
Dose adjustments	Unknown	22
Utilities	Large in RET-mutant MTC, Small in RET fusion-positive TC	23
Other areas of uncertainty: • Clinical effectiveness evidence limitations • RET-mutant MTC population – limitations of MAIC • RET fusion-positive TC population – limitations of naïve unadjusted ITC • Selpercatinib safety evidence	Unknown	8, 11 12-13 14-15 41

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; MAIC, matched-adjusted indirect comparison; ITC, indirect treatment comparison

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Thank you.

Selpercatinib for untreated advanced thyroid cancer with *RET* alterations

Supplementary appendix

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Decision problem (1)

Company used any-line population data for cost-effectiveness model

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	***RET*-mutant MTC** Adults and adolescents 12 years and older with untreated advanced *RET*-mutant MTC who require systemic therapy	***RET*-mutant MTC** As per scope	***RET*-mutant MTC** Company considered that cabozantinib/vandetanib-naïve patients reflected NHS patients with untreated RET-mutant MTC. Company presented data for: • Cabozantanib/vandetanib-naïve population • Any-line population – used for cost-effectiveness model
	***RET* fusion-positive TC** Adults with untreated advanced *RET* fusion-positive thyroid cancer who require systemic therapy	***RET* fusion-positive TC** Adults and adolescents aged 12 years and older included, as per CHMP opinion	***RET* fusion-positive TC** Company presented data for: • Systemic therapy-naïve population • Any-line population – used for cost-effectiveness model

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; CHMP, Committee for Medicinal Products for Human use

Link to Selpercatinib

Decision problem (2)

Company and EAG agree that cabozantinib and lenvatinib are main comparators

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Intervention	Selpercatinib	As per scope	None
Comparators	***RET*-mutant MTC** • cabozantinib (adults) • BSC ***RET* fusion-positive TC** • lenvatinib • sorafenib • BSC	***RET*-mutant MTC** Clinical opinion that 85-95% will receive cabozantinib ***RET* fusion-positive TC** Clinical opinion that 90-95% will receive a MKI and 90-95% of that will be lenvatinib	***RET*-mutant MTC** Agree that cabozantinib is the main comparator ***RET* fusion-positive TC** Agree that lenvatinib is the main comparator
Outcomes	• OS • PFS • Response rate • AEs of treatment • HRQoL	Outcomes from scope all included	None

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; MKI, multikinase inhibitor; BSC, best supportive care; OS, overall survival; PFS, progression-free survival; AE, adverse effect; HRQoL, health-related quality of life

LIBRETTO-001 key efficacy results, *RET*-mutant MTC

Results suggest greater treatment effect in treatment-naïve population

Outcome	*RET*-mutant MTC cabozantinib/vandetanib-naïve (n=143)		*RET*-mutant MTC any-line (n=295)	
	IRC-assessed (n=143)	Investigator-assessed (n=143)	IRC-assessed (n=295)	Investigator-assessed (n=295)
ORR, n (%)	118 (82.5)	[redacted]	[redacted]	NR
CR, n (%)	34 (23.8)	[redacted]	[redacted]	NR
PR, n (%)	84 (58.7)	[redacted]	[redacted]	NR
Median PFS, months (range)	NE (53.1 to NE)	[redacted]	[redacted]	NR
PFS rate ≥12 months (95% CI)	91.1 (84.8 to 94.8)	[redacted]	[redacted]	NR
PFS rate ≥24 months (95% CI)	82.5 (74.8 to 88.0)	[redacted]	[redacted]	NR
PFS rate ≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
PFS rate ≥48 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
Median OS, months (range)	[redacted]		[redacted]	
OS rate ≥12 months (95% CI)	[redacted]		[redacted]	
OS rate ≥24 months (95% CI)	[redacted]		[redacted]	
OS rate ≥36 months (95% CI)	[redacted]		[redacted]	
OS rate ≥48 months (95% CI)	[redacted]		[redacted]	

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; ORR, overall response rate; CR, complete response; PR, partial response; OS, overall survival; PFS, progression-free survival; CI, confidence intervals; NE, not estimable; IRC, independent review committee

LIBRETTO-531 key efficacy results, *RET*-mutant MTC

Results suggest better outcomes with selpercatinib

Outcome	Selpercatinib (n=193)	Physician's choice (n=98)
ORR, n (% [95% CI])	134 (69.4 [62.4 to 75.8])	38 (38.8 [29.1 to 49.2])
Complete response, n (%)	23 (11.9)	4 (4.1)
Partial response, n (%)	111 (57.5)	34 (34.7)
Median DoR (range), months	[redacted]	[redacted]
Hazard ratio (95% CI); p-value	[redacted]	
Patients who progressed or died, n (%)	26 (13.5)	33 (33.7)
Median PFS, months (range)	NE (NE to NE)	16.8 (12.2 to 25.1)
Hazard ratio (95% CI); p-value		0.28 (0.16 to 0.48); p<0.001
PFS rate ≥12 months (95% CI)	86.8 (79.8 to 91.6)	65.7 (51.9 to 76.4)
PFS rate ≥24 months (95% CI)	76.4 (66.5 to 83.8)	37.2 (21.9 to 52.6)
Median TFFS, months (range)	NE (NE to NE)	13.9 (11.3 to 25.1)
Hazard ratio (95% CI); p-value		0.25 (0.15 to 0.42); p<0.001
Patients who died, n (%)	8 (4.1)	10 (10.2)
Median OS, months (range)	NE (NE to NE)	NE (29.77 to NE)
Hazard ratio (95% CI)		[redacted]
OS rate ≥12 months (95% CI)	[redacted]	[redacted]
OS rate ≥24 months (95% CI)	[redacted]	[redacted]

Patients randomised to physician's choice could receive selpercatinib on disease progression

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Abbreviations: ORR, overall response rate; DoR, duration of response; PFS, progression-free survival; TFFS, treatment failure-free survival; OS, overall survival; CI, confidence intervals; NE, not estimable

Issue: Selpercatinib safety evidence

Safety evidence different in LIBRETTO-001 and LIBRETTO-501

Background

- Selpercatinib has conditional licence from EMA and MHRA for RET-mutant MTC and conditional licence expected for *RET* fusion-positive TC in systemic therapy-naïve population
- Regulators have requested further efficacy and safety information

EAG comments

***RET*-mutant MTC**

- Frequencies of general and specific types of adverse events (e.g. treatment emergent Grade ≥3 AEs, SAEs and the incidence of fatigue) often lower in LIBRETTO-531 than LIBRETTO-001
- Focusing on LIBRETTO-001 trial any-line patient safety data may over-estimate safety concerns

***RET* fusion-positive TC**

- Safety evidence limited to selpercatinib and only available for any-line population

Abbreviations: EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; MTC, medullary thyroid cancer; TC, follicular thyroid cancer; AE, adverse effects; SAE, serious adverse event

LIBRETTO-001 key efficacy results, *RET* fusion-positive TC

Small number of patients in systemic therapy-naïve group

Outcome	*RET* fusion-positive TC systemic therapy-naïve (n=24)		*RET* fusion-positive TC any-line (n=65)	
	IRC-assessed (n=24)	Investigator-assessed (n=24)	IRC-assessed (n=65)	Investigator-assessed (n=65)
ORR, n (%)	23 (95.8)	[redacted]	[redacted]	NR
CR, n (%)	5 (20.8)	[redacted]	[redacted]	NR
PR, n (%)	18 (75.0)	[redacted]	[redacted]	NR
Median PFS, months (range)	NE (44.2 to NE)	[redacted]	[redacted]	NR
PFS rate ≥12 months (95% CI)	95.2 (70.7 to 99.3)	[redacted]	[redacted]	NR
PFS rate ≥24 months (95% CI)	95.2 (70.7 to 99.3)	[redacted]	[redacted]	NR
PFS rate ≥36 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
PFS rate ≥48 months (95% CI)	[redacted]	[redacted]	[redacted]	NR
Median OS, months (range)		[redacted]		[redacted]
OS rate ≥12 months (95% CI)		[redacted]		[redacted]
OS rate ≥24 months (95% CI)		[redacted]		[redacted]
OS rate ≥36 months (95% CI)		[redacted]		[redacted]

Abbreviations: TC, follicular thyroid cancer; ORR, overall response rate; CR, complete response; PR, partial response; OS, overall survival; PFS, progression-free survival; CI, confidence intervals; NE, not estimable; IRC, independent review committee

ITC: baseline characteristics, *RET*-mutant MTC

Differences in ECOG status and prior treatment

Characteristic	LIBRETTO-001	EXAM	
	Selpercatinib	Cabozantinib	Placebo
	RET-mutant MTC any-line (n=295)	*RET*-mutant MTC (n=107)	Any *RET* status MTC (n=219)	Any *RET* status MTC (n=111)
Age, median (range) years	58 (15 to 90)	55 (20 to 86)	55 (20 to 86)	55 (21 to 79)
≥65 years, n (%)	[redacted]	23 (21.5)	47 (21.5)	25 (22.5)
Male, n (%)	180 (61.0)	73 (68.2)	151 (68.9)	70 (63.1)
White, n (%)	[redacted]	NR	NR	NR
Asian, n (%)	[redacted]	NR	NR	NR
ECOG PS≥1, n (%)	184 (62.4)	41 (38.3)	95 (43.4)	55 (49.5)
RET M918T mutation-positive, n (%)	[redacted]	NR (74.6)	75 (52.8)	43 (58.9)
Received prior kinase inhibitor, n (%)	[redacted]	23 (21.5)	44 (20.1)	24 (21.6)

In MAICs, company adjusted for age, weight, ECOG performance score, sex, smoking status, RET M918T mutation status and prior MKI treatment.

Link to RET-mutant MTC: indirect treatment comparison – methods

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Abbreviations: ITC, indirect treatment comparison; MTC, medullary thyroid cancer; ECOG PS; Eastern Cooperative Oncology Group performance status; NR, not reported

ITC: Baseline characteristics, *RET* fusion-positive TC

Differences in ECOG performance status, median time from initial diagnosis and prior treatment

Characteristic	LIBRETTO-001	SELECT		DECISION	
	Selpercatinib	Lenvatinib	Placebo	Sorafenib	Placebo
	RET fusion-positive any-line TC (n=65)	Any *RET* status any-line TC (n=261)	Any *RET* status any-line TC (n=131)	Any *RET* status systemic therapy-naïve TC (n=207)	Any *RET* status systemic therapy-native TC (n=210)
Age, median (range) years	59 (20 to 88)	64 (27 to 89)	61 (21 to 81)	63 (24 to 82)	63 (30 to 87)
Male, n (%)	32 (49.2)	125 (47.9)	75 (57.3)	104 (50.2)	95 (45.2)
White, n (%)	[redacted]	208 (79.7)	103 (78.6)	123 (59.4)	128 (61.0)
Asian, n (%)	[redacted]	46 (17.6)	24 (18.1)	47 (22.7)	52 (24.8)
ECOG PS≥1, n (%)	40 (61.5)	117 (44.8)	63 (48.1)	76 (36.7)	80 (38.1)
Median (range) time from initial diagnosis, months	[redacted]	66 (0.4 to 573.6)	73.9 (6.0 to 484.8)	66.2 (3.9 to 362.4)	66.9 (6.6 to 401.8)
Received prior kinase inhibitor, n (%)	[redacted]	66 (25.3)	27 (20.6)	0	0

Patient *RET* fusion status was unknown in the SELECT and DECISION trials

Link to RET fusion-positive TC: ITC methods

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Abbreviations: ITC, indirect treatment comparison; TC, follicular thyroid cancer; ECOG PS; Eastern Cooperative Oncology Group performance status

How company incorporated evidence into model

Input and evidence sources

Input	RET-mutant MTC: assumption and evidence source
Baseline characteristics	**RET-mutant MTC:** Any-line MTC population, LIBRETTO-001 **RET fusion-positive TC:** Any-line RET-fusion-positive TC population, LIBRETTO-001
Utilities	Fordham et al 2015 vignette study: see key issue HRQoL reductions for people experiencing Grade≥3 AEs
Costs	Drug costs from BNF Dose adjustments made to account for treatment toxicity (see key issue) Time on treatment: assumed equal to PFS for cabozantinib and lenvatinib. For selpercatinib, delay in treatment discontinuation equal to mean time on post-progression treatment observed in LIBRETTO-001 systemic therapy-naïve populations.
Healthcare resource use	BSC comprised routine care and monitoring – equivalent in progression-free and progressed disease health states, sourced from NHS Cost Collection. Palliative care costs sourced from TA516, PSSRU and NHS Cost Collection. Administration (pharmacy time) and monitoring costs (ECGs) from NHS Cost Collection. Diagnostic tests for RET included in line with TA911.

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Abbreviations: AE, adverse event, HRQoL, health-related quality of life; BNF, British National Formulary; PFS, progression-free survival; BSC, best supportive care; ECG, electrocardiogram

Treatment effectiveness and extrapolation in the model (1)

Key issues focus on selpercatinib OS (both populations) and cabozantinib OS

RET-mutant MTC

Treatment	OS - data source	OS - method	PFS – data source	PFS - method
Selpercatinib	Propensity score weighted LIBRETTO-001 trial OS K-M data for RET-mutant any-line population	Stratified Weibull distribution	Propensity score weighted LIBRETTO-001 trial PFS K-M data for RET-mutant any-line population	Loglogistic distribution
Cabozantinib	Selected BSC extrapolation	Apply HR reported by Schlumberger	Unweighted cabozantinib EXAM trial PFS K-M data for RET-mutant population	Loglogistic distribution
BSC	Unweighted EXAM trial placebo arm OS K-M data for RET M918T-positive population	Stratified Weibull distribution	Unweighted placebo EXAM trial PFS K-M data for RET-mutant population	Loglogistic distribution

Treatment effectiveness and extrapolation in the model (2)

Key issues focus on selpercatinib OS (both populations) and cabozantinib OS

RET fusion-positive TC

Treatment	OS – data source	OS - method	PFS – data source	PFS - method
Selpercatinib	LIBRETTO-001 trial, selpercatinib arm (RET fusion-positive TC, any-line), OS K-M	Piecewise exponential distribution	LIBRETTO-001 trial PFS K-M data for RET fusion-positive any-line TC population	Stratified Weibull distribution
Lenvatinib	SELECT trial, lenvatinib arm (any-line), RPSFT-adjusted OS K-M	Piecewise exponential distribution	SELECT trial RPSFT-adjusted OS K-M data for patients receiving lenvatinib (any-line)	Stratified Weibull distribution
BSC	SELECT trial, placebo arm (any-line), RPSFT-adjusted OS K-M data	Piecewise exponential distribution	SELECT trial RPSFT-adjusted OS K-M data for patients receiving placebo (any-line)	Stratified Weibull distribution

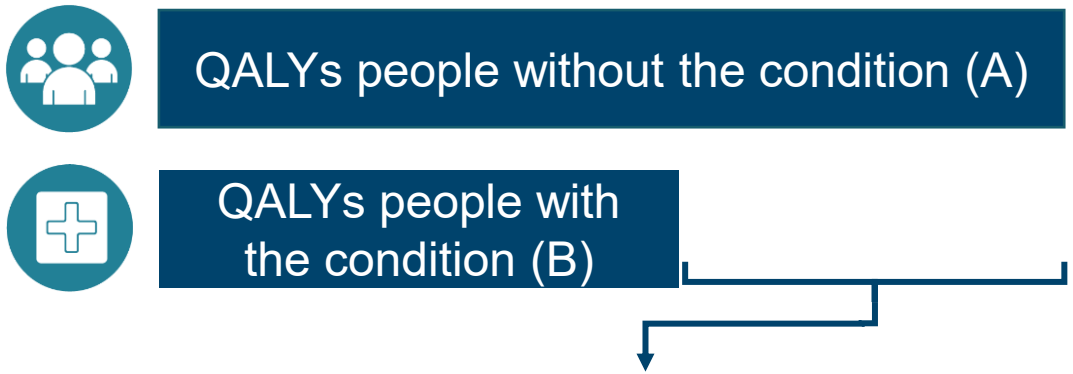
OS extrapolations: *RET*-mutant MTC population

Abbreviations: KM, Kaplan-Meier; BSC, best supportive care

Link to Key Issue: Selpercatinib overall survival
Key Issue: Cabozantinib overall survival

QALY weightings for severity - background

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Link to Key issue: QALY weightings for severity

Abbreviations: QALY, quality-adjusted life year