Selpercatinib (RET-mutant medullary thyroid cancer, first-line therapy)

Benefit assessment according to §35a SGB V[1] (expiry of the decision)

EXTRACT

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the patient organization 'Bundesverband Schilddrüsenkrebs – Ohne Schilddrüse leben e. V.' for participating in the written exchange and for their support. The respondent and 'Bundesverband Schilddrüsenkrebs – Ohne Schilddrüse leben e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AWMF	Association of the Scientific Medical Societies
BICR	blinded independent central review
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTC	medullary thyroid cancer
NRS	Worst Pain numeric rating scale
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
RET	rearranged during transfection
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug selpercatinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 28 May 2025.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. That dossier was sent to IQWiG on 04 October 2022. In that procedure, the G-BA issued a resolution on 16 March 2023 to limit the period of validity of the resolution to 1 June 2025. The validity period was limited as further data relevant for the assessment of the added benefit were to be expected from the LIBRETTO-531 study.

Research question

The aim of this report is to assess the added benefit of selpercatinib compared with vandetanib or cabozantinib as the appropriate comparator therapy (ACT) in adults and adolescents aged 12 years and older with advanced rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC). The subject of this benefit assessment are patients undergoing first-line therapy. The assessment of selpercatinib in adults and adolescents aged 12 years and older with advanced RET-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib has already been conducted (see dossier assessment A21-28 as well as resolution and justification of the G-BA) and is not the subject of this benefit assessment.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of selpercatinib

Therapeutic indication	**ACT**[a]
Adults and adolescents 12 years and older with advanced RET-mutant MTC; first-line therapy	vandetanib or cabozantinib[b]

a. Presented is the ACT specified by the G-BA.
b. When determining the ACTs, according to the G-BA, it is assumed that curative treatment measures and local treatment options are no longer considered. It is also assumed, according to the G-BA, that, based on their symptoms, patients are indicated for systemic antineoplastic therapy and therefore a 'watch and wait' strategy, among others, is not an option.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer; RET: rearranged during transfection

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Randomized controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The RCT LIBRETTO-531 was included in this benefit assessment.

The LIBRETTO-531 study is an ongoing, open-label RCT comparing selpercatinib with cabozantinib or vandetanib, each as monotherapy. Enrolled were patients aged 12 years and older with unresectable, locally advanced and/or metastatic RET-mutant MTC and no prior history of treatment with kinase inhibitors for advanced/metastatic disease. Patients with mixed histology were eligible to participate in the study if MTC was the dominant histology.

Evidence of RET status had to be conducted by a certified laboratory. In regions where no suitable RET test was available, patients were offered a company-supported testing option to determine tumour RET status after obtaining their prior consent.

Another prerequisite for inclusion in the study was an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. Patients who had previously taken kinase inhibitors for less than 7 days were allowed to participate in the study with the consent of the company, provided that the reason for discontinuation was neither intolerance nor disease progression. Prior systemic therapy (with drugs other than kinase inhibitors) or radiation therapy conducted more than 14 months prior to enrolment in the study was allowed.

The study included a total of 291 patients, randomized in a 2:1 ratio either to treatment with selpercatinib (N = 193) or treatment with cabozantinib or vandetanib) (N = 98). Whether a patient would receive cabozantinib or vandetanib upon assignment to the comparator group was determined by the investigator for each patient prior to randomization. Randomization was stratified according to RET mutation type (M918T versus others) and according to the foreseen treatment in case of inclusion in the comparator group (cabozantinib versus vandetanib). Patients in the comparator group were not permitted to switch from cabozantinib to vandetanib during the study. A switch from vandetanib to cabozantinib was possible in exceptional situations where vandetanib was not available, subject to certain conditions.

Treatment with the study medication was continued until disease progression was confirmed by a blinded independent central review (BICR), unacceptable toxicity occurred, or until death. Patients in the comparator group who discontinued treatment due to radiological disease progression and had received cabozantinib or vandetanib were able to switch to selpercatinib.

Treatment with selpercatinib, cabozantinib and vandetanib largely concurred with the specifications in the respective summary of product characteristics (SmPC). Deviating from the recommendation in the SmPC, selpercatinib administration was also possible in the study after disease progression if, in the assessment of the investigator, there was still a clinical benefit.

The primary outcome of LIBRETTO-531 was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Data cuts

Three data cuts were available for the LIBRETTO-531 study. Analogous to the company's approach, the analyses on the data cut from 11 March 2024 were used for the benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for LIBRETTO-531.

There was a low risk of bias for the results of the outcome overall survival. The results for the outcomes of the morbidity and health-related quality of life categories, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), pain (Worst Pain numeric rating scale [NRS]) and the EQ-5D visual analogue scale (VAS), had a high risk of bias. This was due to lack of blinding, as the outcomes are recorded subjectively by the patients. Furthermore, the proportion of missing questionnaires increased sharply over the course of the study and differed between the treatment arms. These shortened observations might have had potentially informative reasons, partly caused by the linking of the questionnaire recording to the study treatment or disease progression.

There was a high risk of bias for the results of the outcome discontinuation due to adverse events (AEs), as the unblinded study design involved a subjective decision for treatment discontinuation. The certainty of results was additionally limited by the fact that treatment might also be discontinued for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion of 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

For the results in the side effects outcome category, the high risk of bias was due to the shortened observations for potentially informative reasons with differing observation periods. These result from the fact that the recording of side effects was linked to the end of the study

treatment. In addition, the unblinded study design led to a high risk of bias in the non-severe/non-serious side effects due to the subjective recording of outcomes.

Note on the certainty of conclusions regarding various outcomes

The risk of bias for the results for the outcomes stomatitis (Preferred Term [PT], AEs), mucosal inflammation (PT, AEs) and palmar-plantar erythrodysaesthesia syndrome (PT, AEs) was initially rated as high. Despite a high risk of bias, the results for these outcomes were considered to have a high certainty of results. This was due to the size of the respective effects and the early occurrence of the events over time. For the outcomes mentioned, the Kaplan-Meier curves show that events occurred right at the start in the comparator arm and the curve drops sharply, while it remains stable in the intervention arm.

Results

Mortality

Overall survival

A statistically significant difference between the treatment arms was shown for the outcome overall survival. There is an indication of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

A statistically significant difference in favour of selpercatinib was shown for the EORTC QLQ-C30 scales fatigue, nausea and vomiting, pain, insomnia, appetite loss and diarrhoea. In each case there is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Pain (Worst Pain NRS)

A statistically significant difference in favour of selpercatinib was shown for the outcome pain (Worst Pain NRS). There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Health status (EQ-5D VAS)

A statistically significant difference in favour of selpercatinib was shown for the health status outcome. There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Health-related quality of life

EORTC QLQ-C30 (global health status, role functioning, emotional functioning, cognitive functioning and social functioning)

A statistically significant difference in favour of selpercatinib was shown for the EORTC QLQ-C30 scales global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

A statistically significant difference in favour of selpercatinib was shown for the EORTC QLQ-C30 physical functioning scale. An effect modification for the characteristic age was found for the physical functioning scale. There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib for patients < 65 years. For patients ≥ 65 years, there is no hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib; an added benefit is therefore not proven for this patient group.

Side effects

Serious AEs (SAEs)

A statistically significant difference in favour of selpercatinib was shown for the outcome SAEs. There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

A statistically significant difference in favour of selpercatinib was shown for the outcome SAEs. There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

Discontinuation due to AEs

A statistically significant difference in favour of selpercatinib was shown for the outcome discontinuation due to AEs. There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE)

No suitable data were available for the outcome PRO-CTCAE. There is no hint of greater or lesser harm of selpercatinib in comparison with cabozantinib or vandetanib; greater or lesser harm is therefore not proven.

Specific AEs

Gastrointestinal disorders (System Organ Class [SOC], AEs), dry mouth (PT, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), stomatitis (PT, AEs), asthenia (PT, AEs), mucosal inflammation (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), palmar-plantar erythrodysaesthesia syndrome (PT, AEs), alanine aminotransferase increased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs)

A statistically significant difference in favour of selpercatinib was shown for each of the outcomes gastrointestinal disorders (SOC, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), asthenia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs). There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

A statistically significant difference in favour of selpercatinib was shown for each of the outcomes stomatitis (PT, AEs), mucosal inflammation (PT, AEs) and palmar-plantar erythrodysaesthesia syndrome (PT, AEs). There is an indication of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

A statistically significant difference to the disadvantage of selpercatinib was shown for each of the outcomes dry mouth (PT, AEs) and alanine aminotransferase increased (PT, severe AEs). There is a hint of greater harm of selpercatinib in comparison with cabozantinib or vandetanib.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Overall, the positive effects of selpercatinib clearly outweigh those of the ACT in all outcome categories in patients with advanced RET-mutant MTC.

In particular, there is an indication of a major added benefit for the outcome overall survival, and consistent positive effects for the majority of scales used to record health-related quality

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

of life, with hints of an added benefit of major extent. In addition, there are positive effects on patient-reported symptoms.

The positive effects also predominate when considering the outcomes in the side effects category, particularly with a hint of lesser harm of major extent in the overall rate of severe AEs.

In contrast, there are isolated negative effects for specific AEs, which, however, do not call into question the major extent of the added benefit.

Table 3 shows a summary of probability and extent of the added benefit of selpercatinib.

Table 3: Selpercatinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults and adolescents 12 years and older with advanced RET-mutant MTC; first-line therapy	vandetanib or cabozantinib[b]	Indication of major added benefit[c, d]

a. Presented is the ACT specified by the G-BA.
b. When determining the ACTs, according to the G-BA, it is assumed that curative treatment measures and local treatment options are no longer considered. It is also assumed, according to the G-BA, that, based on their symptoms, patients are indicated for systemic antineoplastic therapy and therefore a 'watch and wait' strategy, among others, is not an option.
c. Patients with an ECOG PS of 0 to 2 were included in LIBRETTO-531. However, the number of patients with ECOG PS 2 was a maximum of 5, so it remains unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.
d. Only one patient under the age of 18 was included in LIBRETTO-531. It remains unclear whether the observed effects can be transferred to patients under 18 years.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer; RET: rearranged during transfection

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of selpercatinib compared with cabozantinib or vandetanib as the appropriate comparator therapy (ACT) in patients aged 12 years and older with advanced rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC).

The subject of this benefit assessment are patients undergoing first-line therapy. The assessment of selpercatinib in adults and adolescents aged 12 years and older with advanced RET-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib has already been conducted (see dossier assessment A21-28 [3] as well as resolution [4] and justification of the G-BA [5]) and is not the subject of this benefit assessment.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of selpercatinib

Therapeutic indication	**ACT**[a]
Adults and adolescents 12 years and older with advanced RET-mutant MTC; first-line therapy	vandetanib or cabozantinib[b]

a. Presented is the ACT specified by the G-BA.
b. When determining the ACTs, according to the G-BA, it is assumed that curative treatment measures and local treatment options are no longer considered. It is also assumed, according to the G-BA, that, based on their symptoms, patients are indicated for systemic antineoplastic therapy and therefore a 'watch and wait' strategy, among others, is not an option.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer; RET: rearranged during transfection

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study lists on selpercatinib (status: 6 March 2025)
- Bibliographical literature search on selpercatinib (last search on 6 March 2025)
- Search of trial registries/trial results databases for studies on selpercatinib (last search on 6 March 2025)
- Search on the G-BA website for selpercatinib (last search on 6 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on selpercatinib (last search on 16 June 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
J2G-MC-JZJB (LIBRETTO-531[d])	yes	yes	no	yes [6-8]	yes [9-11]	yes [12,13]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the LIBRETTO-531 study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LIBRETTO-531	RCT, open-label, parallel	Patients (≥ 12 years) ▪ with advanced RET-mutant MTC[b] ▪ ECOG PS 0–2	▪ selpercatinib (N = 193) ▪ Comparator therapy (N = 98) ▫ cabozantinib (N = 73) ▫ vandetanib (N = 25)	▪ Screening: up to 42 days ▪ Treatment: until disease progression[c], unacceptable toxicity, decision by the investigator or the patient, death, or at most 6 years[d] ▪ Observation[e]: outcome-specific, at most until death, lost to follow-up or the study end	119 centres in Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, India, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, Taiwan, United Kingdom, United States 2/2020–ongoing[f] Data cut-offs: ▪ 22 May 2023[g] ▪ 11 March 2024[h]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Histologically or cytologically confirmed, unresectable, locally advanced and/or metastatic MTC and no prior history of treatment with kinase inhibitors for advanced/metastatic disease. Prior kinase inhibitor therapy of < 7 days before the study started, and discontinued for reasons other than intolerance or disease progression, was allowed with approval by the company.
c. The study treatment could be continued until disease progression was confirmed according to BICR. Continuation of treatment beyond suspected radiological progression was possible if patients benefited from it. Patients from the comparator arm were allowed to cross over to the selpercatinib arm in the event of BICR-confirmed radiographic disease progression, provided they had discontinued cabozantinib or vandetanib and had not received any other systemic therapy since.
d. The total duration of the study is limited to the occurrence of approximately 125 events for the outcome of overall survival or a maximum of 6 years from the first visit of the first patient.
e. Outcome-specific information is described in Table 8.
f. Expected end of study: 28 February 2026
g. Prespecified interim analysis after the occurrence of 56 PFS events.
h. According to information provided by the company in Module 4 B, this data cut-off was conducted for the annual renewal of the conditional marketing authorization (see running text for further explanation).

AE: adverse event; BICR: blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MTC: medullary thyroid cancer; N: number of randomized (included) patients; PFS: progression-free survival; RCT: randomized controlled trial; RET: rearranged during transfection

Table 7: Characteristics of the intervention – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study	Intervention	Comparison[a]
LIBRETTO-531	selpercatinib (28-day cycle): ▪ Adults: 160 mg, twice daily, orally ▪ Adolescents (weight-dependent dosage): 92 mg/m² BSA (maximum 160 mg), twice-daily, orally	cabozantinib (28-day cycle): ▪ Adults: 140 mg, once daily, orally ▪ Adolescents (weight-dependent dosage): 40 mg/m² BSA, once daily, orally or vandetanib (28-day cycle): ▪ Adults: 300 mg[b], once daily, orally
	Dose modification[c]: ▪ Dose reduction (by a maximum of 2 dose levels) and treatment interruptions were permitted due to toxicities	
	Disallowed prior treatment ▪ Systemic kinase inhibitors[d] ▪ Medication that causes QTc prolongation ▪ Participation in a clinical study involving an investigational product within the last 30 days[e] **Concomitant treatment** ▪ Standard supportive treatments according to institutional guidelines and at the discretion of the investigator **Prohibited concomitant treatment** ▪ Other systemic tumour therapies (including immunotherapies) ▪ Haematopoietic growth factors for prophylaxis in Cycle 1 ▪ Drugs with immunosuppressive properties ▪ Other investigational drugs ▪ Tumour resection or radiotherapy[f] The following concomitant treatments were to be avoided: ▪ selpercatinib arm / vandetanib arm: ▫ Strong inhibitors or inducers of CYP3A4 ▫ Medication that causes QTc prolongation ▪ selpercatinib arm: ▫ CYP2C8-sensitive substrates, proton pump inhibitors and H_2 receptor antagonists	

Table 7: Characteristics of the intervention – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study	Intervention	Comparison[a]
a. The choice of cabozantinib or vandetanib for each patient was made by the investigator prior to randomization. A switch from cabozantinib to vandetanib or from vandetanib to cabozantinib during the study was not planned (however, in exceptional cases, a switch from vandetanib to cabozantinib was possible if vandetanib was not available). b. For patients with moderate renal insufficiency (creatinine clearance between 30 and 50 mL/min), a starting dose of 200 mg was planned for the vandetanib arm. c. A dose reduction was permitted for selpercatinib, cabozantinib and vandetanib if CTCAE v5.0 grade 2 or grade ≥ 3 AEs occurred that could not be resolved within 48 hours with appropriate treatment or were considered intolerable. At dose level 2, treatment had to be discontinued if toxicity reoccurred. A re-escalation of the dose to the next higher level was permitted, provided that the triggering AE had been resolved. An interruption of > 42 days due to toxicities related to the study medication led to study discontinuation. d. Prior kinase inhibitor therapy of < 7 days before the study started, and discontinued for reasons other than intolerance or disease progression, was allowed with approval by the company. e. 4 months for studies conducted in Japan or 3 months for studies conducted in the United Kingdom. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed. f. Palliative radiotherapy or surgery for bone metastases allowed. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; CYP2C8: cytochrome P450 2C8; CYP3A4: cytochrome P450 3A4; BSA: body surface area; QTc: frequency-corrected QT interval; RCT: randomized controlled trial		

The LIBRETTO-531 study is an ongoing, open-label RCT comparing selpercatinib with cabozantinib or vandetanib, each as monotherapy. Enrolled were patients aged 12 years and older with unresectable, locally advanced and/or metastatic RET-mutant MTC and no prior history of treatment with kinase inhibitors for advanced/metastatic disease. Patients with mixed histology were eligible to participate in the study if MTC was the dominant histology.

Evidence of RET status had to be conducted by a certified laboratory. In regions where no suitable RET test was available, patients were offered a company-supported testing option to determine tumour RET status after obtaining their prior consent. In addition, all molecular pathology reports confirming the presence of a valid RET alteration were reviewed by the sponsor prior to inclusion in the study. The provision of an unstained tumour tissue sample in a quantity sufficient to allow for retrospective analysis of RET mutation status (for confirmation) was mandatory.

Another prerequisite for inclusion in the study was an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. Patients who had previously taken kinase inhibitors for less than 7 days were allowed to participate in the study with the consent of the company, provided that the reason for discontinuation was neither intolerance nor disease progression. Prior systemic therapy (with drugs other than kinase inhibitors) or radiation therapy conducted more than 14 months prior to enrolment in the study was allowed.

The study included a total of 291 patients, randomized in a 2:1 ratio either to treatment with selpercatinib (N = 193) or treatment with cabozantinib or vandetanib) (N = 98). Whether a patient would receive cabozantinib or vandetanib upon assignment to the comparator group was determined by the investigator for each patient prior to randomization. Randomization was stratified according to RET mutation type (M918T versus others) and according to the foreseen treatment in case of inclusion in the comparator group (cabozantinib versus vandetanib). Patients in the comparator group were not permitted to switch from cabozantinib to vandetanib during the study. A switch from vandetanib to cabozantinib was possible in exceptional situations where vandetanib was not available, subject to certain conditions.

Treatment with the study medication was continued until disease progression was confirmed by a blinded independent central review (BICR), unacceptable toxicity occurred, or until death. Patients in the comparator group who discontinued treatment due to radiological disease progression and had received cabozantinib or vandetanib were able to switch to selpercatinib.

Treatment with selpercatinib, cabozantinib and vandetanib largely concurred with the specifications in the respective summary of product characteristics (SmPC) [14-16]. Deviating from the recommendation in the SmPC, selpercatinib administration was also possible in the study after disease progression if, in the assessment of the investigator, there was still a clinical benefit. Furthermore, the dosage for adolescents in the study deviated from the SmPC. In the study, there was a formula according to which the dose was calculated based on the patient's body surface area, whereas in the SmPC, a limit of 50 kg body weight is the decisive factor for the 2 dose levels of 120 mg and 160 mg twice daily [14]. However, this deviation only affected one patient under the age of 18 in the LIBRETTO-531 study, as all other patients included were older than 18.

The primary outcome of LIBRETTO-531 was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Data cuts

According to information provided by the company in Module 4 B, 2 data cuts were available for LIBRETTO-531:

- Data cut from 22 May 2023: prespecified data cut-off date for the interim analysis after the occurrence of 56 PFS events
- Data cut from 11 March 2024: according to information provided the company in Module 4 B, this data cut-off was conducted for the annual renewal of the conditional marketing authorization

In Module 4 B, the company only presented results for the data cut from 11 March 2024. The company presented the results for the data cut from 22 May 2023 as supplementary information in Appendix 4 G.

Due to the longer observation period compared to the planned interim analyses of 22 May 2023, with the associated higher number of events, and the analyses initiated by external regulatory authorities, the data cut from 11 March 2024 submitted by the company in Module 4 B was used for the assessment.

With regard to the data cut from 11 March 2024 it should be noted that, according to the information in the marketing authorization documents, the conditional marketing authorization included a specific obligation for the company to update the information in the SmPC on efficacy, safety and pharmacokinetics based on the results of LIBRETTO-531. With reference to this, the European Medicines Agency (EMA) requested the company to submit current data on overall survival as soon as it became available. Subsequently, the company submitted data for the outcome of overall survival and analyses for other outcomes for the data cut from 11 March 2024. The company justified the choice of date (11 March 2024) in the assessment report on the grounds that the standard safety update for the Food and Drug Administration (FDA) was prepared at that time. In the dossier, the company submitted analyses for all relevant outcomes for this data cut.

It should also be noted that, according to the information provided in the marketing authorization documents for the annual renewal of the conditional marketing authorization, the company also delivered safety analyses as of 8 May 2024, which thus cover a slightly longer observation period. No results for this date were available in Module 4 B. However, due to the immediate proximity to the data cut which was taken into account, no relevant changes would be expected.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study **Outcome category** **Outcome**	**Planned follow-up**
LIBRETTO-531	
Mortality	
Overall survival	▪ Until the final analysis[a] for the outcome of overall survival or until the end of the study[b] (whichever comes first)
Morbidity	
Symptoms (EORTC QLQ-C30)	▪ Until up to 120 days after the last dose of the study medication
Pain (Worst Pain NRS)	▪ Until 30 days after the last dose of the study medication, but no longer than 1 year after the start of treatment
Health status (EQ-5D VAS)	▪ Until up to 120 days after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30	▪ Until up to 120 days after the last dose of the study medication
Side effects	
All outcomes in the side effects category	▪ Until 30 days after the last dose of the study medication [c, d]

a. After the occurrence of approx. 125 events for the outcome of overall survival.
b. Until a maximum of 6 years after the start of the first study visit of the first patient.
c. After the 30-day follow-up, only SAEs related to the study treatment will be followed up until death, loss to follow-up, or the start of a new cancer treatment (whichever occurs first).
d. Discrepancies between Module 4 B and the study protocol. According to Module 4 B, AEs were monitored for 30 days after the last dose of the study medication or until the start of a new cancer treatment (whichever occurred first).

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; NRS: numeric rating scale; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

With the exception of the outcome pain (recorded using the Worst Pain numeric rating scale [NRS]), the patient-reported outcomes (PROs) for morbidity and health-related quality of life were planned to be followed up for a maximum of 120 days after the last dose of the study medication. For the outcome of pain, follow-up was planned for 30 days after receiving the last dose of the study medication, limited to 1 year after the start of study treatment. The planned follow-up for the outcomes in the side effects category was 30 days after the last dose of the study medication.

The observation periods for outcomes relating to morbidity, health-related quality of life and side effects were systematically shortened, as they were only recorded for the period of treatment with the study medication (plus 30 or 120 days), or even only for the first year of treatment. However, to draw a reliable conclusion on the total study period or the time to

patient death, it would also be necessary to record the side effects for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study **Characteristic** **Category**	**selpercatinib** **N = 193**	**cabozantinib or vandetanib** **N = 98**
Study LIBRETTO-531		
Age [years], mean (SD)	54 (14)	54 (14)
Age (categories), n (%)		
< 18 years	1 (< 1)	0 (0)
18 to < 65 years	143 (74)	72 (73)
≥ 65 years	49 (25)	26 (27)
Sex [F/M], %	40/60	31/69
Family origin, n (%)		
Asian	43 (22)	24 (24)
Black	5 (3)	2 (2)
Caucasian	116 (60)	52 (53)
No data	29 (15)	20 (20)
Disease duration: time between diagnosis and start of the study treatment [months], median [Q1; Q3]	42.7 [15.2; 98.9]	61.6 [20.2; 141.0]
RET test method, n (%)		
NGS	173 (90)	90 (92)
PCR/Sanger sequencing	20 (10)	8 (8)
RET sample type, n (%)		
Blood	15 (8)	7 (7)
Metastatic tumour tissue	80 (42)	44 (45)
Primary tumour tissue	89 (46)	46 (47)
No data	10 (5)	1 (1)
RET mutation, n (%)		
RET M918T mutation	121 (63)	61 (62)
Other RET mutation	72 (37)	37 (38)
Stage of disease, n (%)		
M0	21 (11)	3 (3)
M1	141 (73)	83 (85)
MX	18 (9)	6 (6)
No data	13 (7)	6 (6)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study **Characteristic** **Category**	**selpercatinib** **N = 193**	**cabozantinib or vandetanib** **N = 98**
ECOG PS, n (%)		
0	122 (64)	55 (57)
1	70 (37)	39 (40)
2	0 (0)	3 (3)
Missing	1 (< 1)	1 (1)
Previous cancer treatment		
Surgical procedure	167 (87)	85 (87)
Radiation	58 (30)	39 (40)
Systemic and locoregional therapies	2 (1)	4 (4)
Treatment discontinuation, n (%[a])[b]	25 (13)	75 (77)
Study discontinuation, n (%)	ND[c]	ND[c]

a. Institute's calculation.
b. Common reasons for treatment discontinuation in the intervention vs. the control arm were the following (percentages based on randomized patients): disease progression (4% vs. 34%), AEs (3% vs. 29%). An additional 0% vs. 1% of randomized patients never started treatment. The data also include patients who died during treatment with the study medication (intervention arm: 3% vs. control arm: 6%).
c. No data are available regarding the number of patients who discontinued the study. According to the study documentation, the data provided in Module 4 B on patients who discontinued the study refers to patients who discontinued treatment.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; NGS: next generation sequencing; PCR: polymerase chain reaction; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; RET: rearranged during transfection; SD: standard deviation

The 2 treatment arms were balanced in terms of patients' demographic and clinical characteristics. The patients were 54 years old on average, and there was only one patient under the age of 18. The patients in both treatment arms were predominantly male (60% in the intervention arm and 69% in the comparator arm) and largely of white family origin (60% and 53%). Approximately 63% of patients had the RET mutation M918T and 87% had undergone surgery as part of previous cancer treatment. The median duration of illness was shorter in the intervention arm than in the comparator arm (42.7 months vs. 61.6 months).

Treatment discontinuation occurred in 77% of patients in the comparator arm and thus notably more frequently than in the intervention arm, for which the figure was 13%. No data were available on the proportion of patients who discontinued the study.

Information on the course of the study

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes. No information on the median observation period was available.

Table 10: Information on the course of the study – RCT, direct comparison selpercatinib vs. cabozantinib or vandetanib

Study **Duration of the study phase** **Outcome category/outcome**	**selpercatinib** **N = 193**	**cabozantinib or vandetanib** **N = 98**	
		cabozantinib N = 73	**vandetanib** N = 25
LIBRETTO-531			
Treatment duration [months][a]			
Median [Q1; Q3]		9.2 [3.9; 15.2]	18.8 [9.4; 30.2]
Mean (SD)		10.6 (7.9)	20.4 (13.0)
Treatment duration [months][a]			
Median [Q1; Q3]	24.8 [16.8; 32.9]	11.3 [4.6; 16.8]	
Mean (SD)	24.4 (10.2)	13.1 (10.3)	
Observation period [months]			
Overall survival[b]			
Median [Q1; Q3]	24.7 [17.5; 32.6]	25.0 [17.0; 32.0]	
Morbidity			
Symptoms (EORTC QLQ-C30)			
Median [Q1; Q3]	21.7 [13.9; 28.0]	9.4 [3.8; 16.6]	
Pain (Worst Pain NRS)			
Median [Q1; Q3]	11.8 [11.8; 11.8]	10.1 [3.7; 11.8]	
Health status (EQ-5D VAS)			
Median [Q1; Q3]	21.7 [13.9; 28.0]	9.4 [3.8; 16.6]	
Health-related quality of life (EORTC QLQ-C30)			
Median [Q1; Q3]	21.7 [13.9; 28.0]	9.4 [3.8; 16.6]	
Side effects			
AEs			
Median [Q1; Q3]	23.2 [15.9; 31.8]	11.6 [5.9; 19.2]	
PRO-CTCAE			
Median [Q1; Q3]		No suitable data[c]	

a. Institute's calculation from data in weeks.
b. The observation periods for overall survival and progression-free survival were calculated using the Kaplan-Meier method and inverse censoring.
c. For an explanation, see Section I 4.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; NRS: numeric rating scale; PRO: patient-reported outcome; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

In LIBRETTO-531, the median treatment duration was notably longer in the intervention arm, at 24.8 months, than in the comparator arm, at 11.3 months.

The median observation period for the outcome overall survival was comparable in both study arms (about 25 months). In the other outcome categories, with the exception of pain (recorded using the Worst Pain NRS), the median observation period was notably longer in the intervention arm than in the comparator arm. The reason for this was that the observation period was linked to the treatment period (see Table 8). The median observation period for the outcome of pain was comparable between the intervention arm (11.8 months) and the comparator arm (10.1 months), as the recording of this outcome was limited to a maximum of 1 year after the start of study treatment. However, when looking at the data on the quartiles, there were clear differences in the observation times between the treatment arms. While a quarter of patients in the comparator arm were observed for less than 4 months (Q1: 3.7 months), the observation period for patients in the selpercatinib arm was predominantly 1 year (Q1: 11.8 months).

The differences in observation periods were taken into account when deriving the outcome-specific risk of bias of the results for the outcomes in the categories morbidity, health-related quality of life and side effects.

As explained in the description of the study characteristics, the study documents show that, under certain conditions, patients in the comparator group were allowed to change from vandetanib to cabozantinib in exceptional situations if vandetanib was not available. No information was available on the number of patients who underwent such a change in therapy during the course of the study, nor was it clear from the available data to what extent these changes in therapy within the comparator group were included in the presentation of the observation periods. This regulation was introduced with the protocol amendment dated 6 April 2022 (‘Amendment (f)’ to the study protocol).

Table 11 shows the subsequent therapies patients received after discontinuing the study medication. The information was taken from Module 4 B, Appendix 4 G of the dossier.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study **Type of therapy** **Drug**	**selpercatinib** **N = 193**	**cabozantinib or vandetanib** **N = 98**
LIBRETTO-531		
Patients with disease progression (BICR assessment), n (%)	34 (17.6)	47 (48.0)
	Patients with subsequent therapy	
Total (each subsequent antitumour therapy)[a], n (%)	6 (3.1)	15 (15.3)
Systemic therapy	4 (2.1)	15 (15.3)
selpercatinib[b]	1 (0.5)	11 (11.2)
Investigational product	0 (0)	2 (2.0)
pralsetinib	2 (1.0)	0 (0)
cabozantinib	1 (0.5)	0 (0)
sorafenib	0 (0)	1 (1.0)
vandetanib	0 (0)	1 (1.0)
Surgical procedure	0 (0)	1 (1.0)
Radiation	2 (1.0)	0 (0)
Total (any antitumour therapy after disease progression)[a], n (%)	3 (1.6)	4 (4.1)
Systemic therapy	1 (0.5)	4 (4.1)
selpercatinib[b]	0 (0)	3 (3.1)
cabozantinib	1 (0.5)	0 (0)
vandetanib	0 (0)	1 (1.0)
Surgical procedure	0 (0)	0 (0)
Radiation	2 (1.0)	0 (0)

a. Patients may be counted in more than one type of therapy, but will be counted no more than once within a single type of therapy.
b. The switch to selpercatinib treatment according to the study design is apparently not included in these data, or at most only partially.

BICR: blinded independent central review; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial

According to the information in the study documents, patients received the study medication until disease progression or unacceptable toxicity occurred. Subsequent further antitumour therapy was possible in both study arms. For patients in the comparator arm, it was stated that a switch to the selpercatinib arm was possible in the event of disease progression. The prerequisites for this included adequate haematological, hepatic and renal function, resolution of all cabozantinib- or vandetanib-related toxicities, and continued ECOG PS of 0-2.

Module 4 B did not contain any information on the subsequent therapies used. The only information provided was that 35 patients in the comparator arm with confirmed radiological disease progression switched to treatment with selpercatinib and took at least one dose of selpercatinib.

However, in Appendix 4 G to Module 4 B the company presented analyses of subsequent antineoplastic therapies (see Table 11). The data referred to each subsequent anti-tumour therapy, and to each anti-tumour therapy after disease progression. The company did not provide any further details or explanations. The proportion of patients who underwent subsequent therapy was notably lower in the intervention arm than in the control arm (3.1% versus 15.3%). Selpercatinib was the most common subsequent therapy (11.2%) used in the comparator arm.

It is unclear to what extent the information provided by the company fully represented the use of subsequent therapies in LIBRETTO-531. For example, according to Table 11 only 3 patients in the comparator arm received subsequent antitumour therapy with selpercatinib after disease progression. This contradicts the information provided by the company in Module 4 B, which stated that, as described above, 35 patients switched to treatment with selpercatinib after progression.

The number of subsequent therapies listed in Table 11 also appeared to be very low overall and differed between the 2 study arms. According to data from the company, only 3 patients (approx. 9%) in the intervention arm and 4 patients (approx. 9%) in the comparator arm received subsequent therapy after disease progression. However, if the 35 patients who switched to treatment with selpercatinib after progression are also taken into account, it can be assumed that, unlike in the intervention arm, the vast majority of patients in the comparator arm received subsequent therapy after progression of the disease.

Overall, the drugs used in the study were reflective of the recommendations of the S3 guideline and the National Comprehensive Cancer Network (NCCN) [17,18], according to which , if progression occurs under a TKI in the second line, other TKIs can be used as part of an individual treatment attempt, including selpercatinib, cabozantinib and vandetanib, depending on previous therapy. Furthermore, it seems reasonable that only some patients with progression receive subsequent therapy, as the S3 guideline of the Association of the Scientific Medical Societies (AWMF) states that the majority of patients, even in the advanced stage of metastasis, progress slowly and have a quality of life that is hardly impaired, which is why the mere evidence of metastasis and progression is not an indication for therapy [17]. Against this background, it is understandable that not all patients receive immediate subsequent therapy after progression. The company presented no information regarding this aspect. However, there remains a striking discrepancy in that, based on the available data,

there were notable differences between the study arms with regard to the frequency of use of subsequent therapies.

Given the available data, it remained unclear why there was a notable difference between the intervention arm and the comparator arm in the use of subsequent therapy, including changing to therapy with selpercatinib following disease progression. In particular, it remained unclear whether the same criteria were used in both arms to determine the timing of subsequent therapy, or whether the explicitly planned switch from the comparator arm to treatment with selpercatinib led to earlier and more frequent use of subsequent therapy in the comparator arm.

Overall, however, the unclear points described did not lead to a downgrading of the certainty of conclusions for the results for the outcome overall survival.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
LIBRETTO-531	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for LIBRETTO-531. Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that RET mutations are known oncogenic drivers, particularly in MTC. From the perspective of the company, with reference to section 3.2.4 of Module 3 B, values ranging from 55.8% to 75% can be found in the literature. According to the company, the transferability of the study results to the German health care context was based in particular on the structural equality of the patient characteristics of the study population with the relevant patients in the therapeutic indication in routine care in Germany.

The company described LIBRETTO-531 as an international study that included patients from centres in several European countries (Belgium, France, Greece, Italy, the Netherlands, Poland, Spain, Czech Republic, United Kingdom) in addition to patients from German centres. It stated that the median age of patients in LIBRETTO-531 was 56 years in the selpercatinib arm and 53.5 years in the cabozantinib/vandetanib arm, and that this was within the range of the median age of disease onset in Germany (women: 51 years, men: 55 years). The company described that at 40.4% in the selpercatinib arm and 30.6% in the comparator arm, the proportion of female patients with advanced MTC was smaller than the proportion of female patients with thyroid carcinoma in Germany. It stated that the majority of patients had Caucasian family origins (70.7% and 66.7% respectively) and that this was essentially reflective of the demographic composition of the German population.

Furthermore, from the company's perspective, the treatment mode of the comparator arm with treatment of physician's choice, choosing between cabozantinib and vandetanib, realistically represents the health care situation in Germany (without taking selpercatinib into account).

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
  - Pain, recorded using the Worst Pain NRS
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - Recorded with the EORTC QLQ-C30
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - PRO-CTCAE
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30)	Pain (Worst Pain NRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Specific AEs[b]
LIBRETTO-531	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events (coded according to MedDRA) are considered: gastrointestinal disorders (SOC, AEs), dry mouth (PT, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), stomatitis (PT, AEs), asthenia (PT, AEs), mucosal inflammation (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), palmar-plantar erythrodysaesthesia syndrome (PT, AEs), alanine aminotransferase increased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
c. No suitable data available; for justification see Section I 4.1 of this dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; NRS: numeric rating scale; PRO: patient-reported outcome; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on outcomes

Overall survival

For the outcome overall survival, analyses based on all randomized patients were used. The sensitivity analyses additionally presented by the company in Module 4 B, in which, among other things, patients were censored at the start of a new systemic therapy, including a switch from the comparator arm to the intervention arm, were not relevant for this benefit assessment.

Analyses of patient-reported outcomes on morbidity and health-related quality of life provided by the company

In LIBRETTO-531, symptoms and health-related quality of life were recorded using the EORTC QLQ-C30, pain using a numeric rating scale (Worst Pain NRS) and health status using the EQ-5D VAS.

Analyses based on the EORTC QLQ-C30 (scale range 0 to 100)

In Module 4 B, the company provided analyses for the outcomes symptoms and health-related quality of life (assessed using the EORTC QLQ-C30) for the time to first worsening of symptoms or first improvement of symptoms, based on an increase or reduction of ≥ 10 points versus baseline on the respective symptom scale.

In addition, the company presented the following analyses in Appendix 4 G:

- Time to confirmed deterioration / confirmed improvement in symptoms based on an increase/decrease on the respective symptom scale of ≥ 10 points versus baseline, defined as an increase/decrease on the respective EORTC QLQ-C30 symptom scale of ≥ 10 points versus baseline, confirmed in the subsequent recording.
- Change in the respective symptom scale over time versus baseline (MMRM analysis).

Analyses of the outcome pain based on the Worst Pain NRS (scale range 0 to 10)

The Worst Pain NRS is a scale ranging from 0 to 10 points, where 0 stands for 'no pain' and 10 for 'pain as bad as you can imagine'. With NRS, the survey period covers the last 24 hours and is documented daily by patients. The average weekly values are included in the analysis.

In Module 4 B, the company presented analyses of the time until the first deterioration/improvement, defined as an increase/reduction in the score of ≥ 2 points versus the baseline. The company also presented the results of the analyses up to the time to confirmed deterioration/improvement, defined as the time from randomization to the first increase/first reduction of ≥ 2 points versus baseline, confirmed in the next cycle.

Analyses of the outcome health status recorded using EQ-5D VAS (scale range 0 to 100)

In Module 4 B, the company presented analyses covering the period from randomization to the first deterioration/improvement. A first deterioration/improvement was achieved as soon as a decrease/increase of at least 15 points was measured versus the baseline. In addition, the company presented results in Appendix 4 G on the change in the values collected using the EQ-5D VAS versus baseline (MMRM analysis).

Analyses used for this benefit assessment

Due to the expected progressive course of the disease in the given therapeutic indication, an analysis of the deterioration in health status is primarily relevant for this benefit assessment.

For the outcomes mentioned, the observation times differed notably between the treatment arms (see Table 10). For the pain outcome, assessed using an NRS, the median observation times were comparable, but when considering the quartiles there were clear differences in the distribution of observation times between the 2 study arms. While a quarter of patients

in the comparator arm were observed for less than 4 months (Q1: 3.7 months), the observation period for patients in the selpercatinib arm was predominantly 1 year (Q1: 11.8 months). Due to the different observation periods and different distributions (pain outcome) between the study arms, the analyses submitted by the company on confirmed deterioration were not used for this benefit assessment, but rather the analyses on first deterioration.

For the time to first deterioration responder analyses were used, with the following response criteria applied:

- EORTC QLQ-C30: deterioration ≥ 10 points each (respective scale range 0 to 100)
- Pain (Worst Pain NRS): deterioration of ≥ 2 points (scale range 0 to 10)
- EQ-5D VAS: deterioration of ≥ 15 points (scale range 0 to 100)

The response criterion for the pain outcome (Worst Pain NRS) was prespecified in the statistical analysis plan (SAP), whereas the response criteria for the outcomes symptoms (EORTC QLQ-C30) and health status (EQ-5D VAS) were not prespecified in the study protocol. Since the response criteria used for the analyses correspond to the criteria described in the General Methods of the Institute [1] for response criteria that reflect a change that is perceptible to patients with sufficient certainty, the responder analyses were taken into account for the benefit assessment.

Analyses of patient-reported outcomes for side effects (PRO-CTCAE)

In LIBRETTO-531, side effects were also recorded with the PRO-CTCAE instrument. Overall, the PRO-CTCAE system is a valuable addition to the usual recording and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process for a survey should be planned a priori and carried out transparently. The selection of the individual symptomatic AEs must be transparent, e.g. the recording of all important potential AEs of the drugs in the intervention and the comparator arm. For a comprehensive description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [19].

According to the study documents, the following symptomatic AEs of the PRO-CTCAE system were recorded in LIBRETTO-531:

- Diarrhoea
- Hand-foot syndrome
- Loss of appetite
- Nausea
- Fatigue

- Taste changes
- Mouth or throat sores
- Constipation
- Vomiting
- Headache
- Dry mouth
- Rash
- Acne

According to the study documentation, the decision-making rules for selecting the final symptom group were to select a maximum of 20 items, in order to minimize the burden on patients during the recording. In addition, at least the 5 most common AEs of selpercatinib, cabozantinib and vandetanib that occurred in the relevant clinical studies and were described in the package inserts in the United States were to be included.

The study documents pointed out that there is no official analysis method for the PRO-CTCAE.

The selection process for AEs from the PRO-CTCAE system used in LIBRETTO-531 appeared appropriate, but was not tested further because the data submitted by the company were not suitable for the PRO-CTCAE outcome. The company presented only descriptive analyses of the mean score or mean changes in the score compared to baseline across the individual measurement points, but no analyses comparing the treatment arms. In addition, a meaningful proportion of missing values occurred during the course of the study, which also differed between the 2 study arms, with a notably greater decrease in the comparator arm. Overall, the data presented were not suitable to assess the added benefit of selpercatinib versus the ACT.

Notes on other outcomes presented by the company in Module 4 B

EORTC-IL19

In the study to be included, the EORTC-IL19 was used in addition to the EORTC QLQ-C30 for the recording of health-related quality of life. The EORTC-IL19 concurs with the physical function domain of the EORTC QLQ-C30 (5 questions), but its recording was more common. In LIBRETTO-531, the QLQ-C30 was used to comprehensively record health-related quality of life, with the individual scales representing the various aspects of health-related quality of life. The physical function outcome recorded using the EORTC-IL19 was therefore not additionally considered.

FACT-GP5

In Module 4 B, the company presented analyses for the outcome therapy side-effect burden based on the recording of a single item from the FACT (Functional Assessment of Cancer Therapy)-G questionnaire (item GP5: 'I am bothered by side effects of treatment'). However, recording data on the burden of side effects of therapy via this single item is not meaningful in terms of content. For individual patients, it is often impossible to distinguish whether the stress in a particular case is due to side effects of the treatment or to another cause, such as the symptoms of the underlying disease. For this reason, it is not possible to uniformly record the burden of side effects of the therapy. Therefore, the analyses presented by the company based on the individual question regarding the burden of side effects of the therapy were not suitable for the benefit assessment.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study	Study level	Outcomes									
		Overall survival	Symptoms (EORTC QLQ-C30)	Pain (Worst Pain NRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Specific AEs[b]
LIBRETTO-531	L	L	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[d]	H[d]	H[f]	–[g]	H[c, d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events (coded according to MedDRA) are considered: gastrointestinal disorders (SOC, AEs), dry mouth (PT, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), stomatitis (PT, AEs), asthenia (PT, AEs), mucosal inflammation (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), palmar-plantar erythrodysaesthesia syndrome (PT, AEs), alanine aminotransferase increased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
c. Lack of blinding in subjective recording of outcomes; applies to the other specific AEs for non-severe AEs.
d. Incomplete observations for potentially informative reasons with different observation periods.
e. Marked decrease in questionnaire return rates over the course of the study, which differed between treatment arms.
f. Lack of blinding in the presence of subjective decision on treatment discontinuation.
g. No suitable data available; for reasoning, see Section I 4.1 of this dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NRS: numeric rating scale; PRO: patient-reported outcome; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

There was a low risk of bias for the results of the outcome overall survival.

The results for the outcomes of the categories morbidity and health-related quality of life, recorded using the EORTC QLQ-C30, pain (Worst Pain NRS) and EQ-5D VAS instruments, had a high risk of bias. This was due to lack of blinding, as the outcomes are recorded subjectively by the patients. Furthermore, the proportion of missing questionnaires increased sharply over the course of the study and differed between the treatment arms. These shortened observations might have had potentially informative reasons, partly caused by the linking of the questionnaire recording to the study treatment or disease progression (see Table 8).

There was a high risk of bias for the results of the outcome discontinuation due to AEs, as the unblinded study design involved a subjective decision for treatment discontinuation. The certainty of results was additionally limited by the fact that treatment might also be discontinued for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of treatment may occur after discontinuation for other reasons, the criterion of 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

For the results in the side effects outcome category, the high risk of bias was due to the shortened observations for potentially informative reasons with differing observation periods. These result from the fact that the recording of side effects was linked to the end of the study treatment (see Table 8). In addition, the unblinded study design led to a high risk of bias in the non-severe/non-serious side effects due to the subjective recording of outcomes.

Note on the certainty of conclusions regarding various outcomes

The risk of bias for the results for the outcomes stomatitis (PT, AEs), mucosal inflammation (PT, AEs) and palmar-plantar erythrodysaesthesia syndrome (PT, AEs) was initially rated as high (see above for reasons). Despite a high risk of bias, the results for these outcomes were considered to have a high certainty of results. This was due to the size of the respective effects and the early occurrence of the events over time (see Figure 26, Figure 28 and Figure 30 in I Appendix B.4 of the full dossier assessment). For the outcomes mentioned, the Kaplan-Meier curves show that events occurred right at the start in the comparator arm and the curve drops sharply, while it remains stable in the intervention arm.

I 4.3 Results

Table 15 summarizes the results for the comparison of selpercatinib with cabozantinib or vandetanib in patients aged 12 years and older with advanced RET-mutant MTC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses shown are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study Outcome category Outcome	selpercatinib		cabozantinib or vandetanib		selpercatinib vs. cabozantinib or vandetanib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
LIBRETTO-531					
Mortality					
Overall survival	193	NA 10 (5.2)	98	NA 16 (16.3)	0.28 [0.12; 0.61]: < 0.001
Morbidity					
Symptoms (EORTC QLQ-C30 – time to 1st deterioration)[b]					
Fatigue	193	4.6 [2.73; 7.46] 128 (66.3)	98	1.2 [0.99; 1.91] 68 (69.4)	0.56 [0.41; 0.76]; < 0.001
Nausea and vomiting	193	19.4 [11.01; 24.87] 97 (50.3)	98	2.2 [1.81; 4.63] 56 (57.1)	0.44 [0.32; 0.62]; < 0.001
Pain	193	5.7 [2.89; 11.07] 115 (59.6)	98	1.9 [1.12; 2.63] 65 (66.3)	0.54 [0.39; 0.74]; < 0.001
Dyspnoea	193	27.4 [10.15; NC] 94 (48.7)	98	10.6 [6.47; 22.60] 44 (44.9)	0.79 [0.55; 1.13]; 0.195
Insomnia	193	NA [16.62; NC] 79 (40.9)	98	2.8 [2.10; 19.42] 51 (52.0)	0.55 [0.39; 0.79]; < 0.001
Appetite loss	193	35.9 [19.35; NC] 82 (42.5)	98	2.0 [1.87; 3.71] 64 (65.3)	0.28 [0.20; 0.39]; < 0.001
Constipation	193	2.9 [2.14; 4.47] 131 (67.9)	98	3.7 [1.91; 14.03] 51 (52.0)	1.04 [0.75; 1.45]; 0.795
Diarrhoea	193	NA [10.81; NC] 85 (44.0)	98	2.0 [1.45; 3.25] 58 (59.2)	0.39 [0.28; 0.55]; < 0.001
Pain (Worst Pain NRS) – time to 1st deterioration[c]	193	NA 44 (22.8)	98	9.1 [1.71; NC] 40 (40.8)	0.42 [0.27; 0.65]; < 0.001
Health status (EQ-5D VAS – time to 1st deterioration[d])	193	38.7 [24.87; NC] 72 (37.3)	98	3.7 [2.43; 7.98] 53 (54.1)	0.40 [0.28; 0.58]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study Outcome category Outcome	selpercatinib		cabozantinib or vandetanib		selpercatinib vs. cabozantinib or vandetanib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 – time to 1st deterioration[e]					
Global health status	193	5.4 [3.71; 7.39] 123 (63.7)	98	1.8 [0.99; 1.91] 66 (67.3)	0.53 [0.39; 0.72]; < 0.001
Physical functioning	193	27.6 [11.60; NC] 87 (45.1)	98	2.7 [1.87; 3.68] 61 (62.2)	0.35 [0.25; 0.50]; < 0.001
Role functioning	193	5.8 [3.75; 12.94] 114 (59.1)	98	1.9 [1.02; 2.96] 66 (67.3)	0.49 [0.36; 0.66]; < 0.001
Emotional functioning	193	29.1 [20.30; NC] 81 (42.0)	98	5.2 [2.79; 9.26] 48 (49.0)	0.51 [0.35; 0.74]; < 0.001
Cognitive functioning	193	5.6 [4.21; 9.40] 123 (63.7)	98	4.4 [2.00; 6.47] 59 (60.2)	0.73 [0.53; 0.99]; 0.046
Social functioning	193	9.0 [4.70; 14.65] 110 (57.0)	98	2.2 [1.81; 3.68] 61(62.2)	0.53 [0.38; 0.72]; < 0.001
Side effects					
AEs (supplementary information)	193	0.3 [0.26; 0.30] 192 (99.5)	97	0.2 [0.13; 0.23] 96 (99.0)	–
SAEs	193	NA [33.12; NC] 59 (30.6)	97	30.3 [22.05; NC] 33 (34.0)	0.59 [0.38; 0.92]; 0.017
Severe AEs[f]	193	10.1 [5.06; 12.39] 119 (61.7)	97	1.9 [1.12; 4.60] 79 (81.4)	0.54 [0.40; 0.73]; < 0.001
Discontinuation due to AEs	193	NA 11 (5.7)	97	NA [18.17; NC] 31 (32.0)	0.11 [0.05; 0.23]; < 0.001
PRO-CTCAE			No suitable data[g]		
Gastrointestinal disorders (SOC, AEs)	193	2.3 [1.25; 3.65] 135 (69.9)	97	0.5 [0.30; 0.92] 82 (84.5)	0.53 [0.40; 0.71]; < 0.001
Dry mouth (PT, AEs)	193	NA 70 (36.3)	97	NA 10 (10.3)	3.65 [1.88; 7.09]; < 0.001
Diarrhoea (PT, AEs)	193	NA 54 (28.0)	97	3.0 [1.84; 5.26] 61 (62.9)	0.27 [0.19; 0.40]; < 0.001
Nausea (PT, AEs)	193	NA 22 (11.4)	97	NA [13.73; NC] 34 (35.1)	0.22 [0.12; 0.38]; < 0.001
Vomiting (PT, AEs)	193	NA 19 (9.8)	97	40.0 [NC] 25 (25.8)	0.26 [0.14; 0.47]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study Outcome category Outcome	selpercatinib		cabozantinib or vandetanib		selpercatinib vs. cabozantinib or vandetanib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Stomatitis (PT, AEs)	193	NA 7 (3.6)	97	NA 19 (19.6)	0.14 [0.06; 0.33]; < 0.001
Asthenia (PT, AEs)	193	NA 26 (13.5)	97	NA [33.08; NC] 27 (27.8)	0.37 [0.21; 0.63]; < 0.001
Mucosal inflammation (PT, AEs)	193	NA 14 (7.3)	97	NA 24 (24.7)	0.23 [0.12; 0.45]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	193	NA [19.61; NC] 84 (43.5)	97	1.0 [0.59; 0.99] 78 (80.4)	0.27 [0.20; 0.37]; < 0.001
Palmar-plantar erythrodysaesthesia syndrome (PT, AEs)	193	NA 7 (3.6)	97	NA [2.53; NC] 42 (43.3)	0.06 [0.03; 0.13]; < 0.001
Alanine aminotransferase increased (PT, severe AEs[f])	193	NA 21 (10.9)	97	NA 2 (2.1)	5.16 [1.21; 22.07]; 0.014
Metabolism and nutrition disorders (SOC, severe AEs[f])	193	NA 12 (6.2)	97	NA [30.29; NC] 19 (19.6)	0.19 [0.09; 0.41]; < 0.001
Nervous system disorders (SOC, severe AEs[f])	193	NA 5 (2.6)	97	NA 7 (7.2)	0.29 [0.09; 0.93]; 0.027
Blood and lymphatic system disorders (SOC, severe AEs[f])	193	NA 4 (2.1)	97	NA 7 (7.2)	0.17 [0.05; 0.60]; 0.002
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	193	NA 3 (1.6)	97	NA 5 (5.2)	0.17 [0.04; 0.74]; 0.008

a. Cox model with stratification variables RET mutation and indicated therapy; p-value: stratified log-rank test.
b. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. A pain score increase (Worst Pain NRS) of ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10).
d. An EQ-5D VAS score decrease of ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. Operationalized as CTCAE grade ≥ 3.
g. No suitable data available; for reasoning, see Section I 4.1 of this dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Study Outcome category Outcome	selpercatinib		cabozantinib or vandetanib		selpercatinib vs. cabozantinib or vandetanib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; NRS: numeric rating scale; PRO: patient-reported outcome; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; RET: rearranged during transfection; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the results for the outcome overall survival. Due to the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the results for the outcomes in the categories of morbidity, health-related quality of life and side effects. This does not apply to the results for the outcomes stomatitis (PT, AEs), mucosal inflammation (PT, AEs) and palmar-plantar erythrodysaesthesia syndrome (PT, AEs). Despite a high risk of bias due to the size of the effects and the early occurrence of events over time (see Section I 4.2), there are at most indications, for example of an added benefit, for these outcomes.

Mortality

A statistically significant difference between the treatment arms was shown for the outcome overall survival. There is an indication of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

A statistically significant difference in favour of selpercatinib was shown for the EORTC QLQ-C30 scales fatigue, nausea and vomiting, pain, insomnia, appetite loss and diarrhoea. In each case there is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Pain (Worst Pain NRS)

A statistically significant difference in favour of selpercatinib was shown for the outcome pain (Worst Pain NRS). There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Health status (EQ-5D VAS)

A statistically significant difference in favour of selpercatinib was shown for the health status outcome. There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning)

A statistically significant difference in favour of selpercatinib was shown for the EORTC QLQ-C30 scales global health status, role functioning, emotional functioning, cognitive functioning and social functioning. There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

A statistically significant difference in favour of selpercatinib was shown for the EORTC QLQ-C30 physical functioning scale. For the physical functioning scale, there was an effect modification for the characteristic of age (see Section I 4.4). There is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib for patients < 65 years. For patients ≥ 65 years, there is no hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib; an added benefit is therefore not proven for this patient group.

Side effects

SAEs

A statistically significant difference in favour of selpercatinib was shown for the outcome SAEs. There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of selpercatinib was shown for the outcome SAEs. There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

Discontinuation due to AEs

A statistically significant difference in favour of selpercatinib was shown for the outcome discontinuation due to AEs. There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

PRO-CTCAE

No suitable data were available for the outcome PRO-CTCAE. There is no hint of greater or lesser harm of selpercatinib in comparison with cabozantinib or vandetanib; greater or lesser harm is therefore not proven.

Specific AEs

Gastrointestinal disorders (SOC, AEs), dry mouth (PT, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), stomatitis (PT, AEs), asthenia (PT, AEs), mucosal inflammation (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), palmar-plantar erythrodysaesthesia syndrome (PT, AEs), alanine aminotransferase increased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs)

A statistically significant difference in favour of selpercatinib was shown for each of the outcomes gastrointestinal disorders (SOC, AEs), diarrhoea (PT, AEs), nausea (PT, AEs), vomiting (PT, AEs), asthenia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), metabolism and nutrition disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), blood and lymphatic system disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs). There is a hint of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

A statistically significant difference in favour of selpercatinib was shown for each of the outcomes stomatitis (PT, AEs), mucosal inflammation (PT, AEs) and palmar-plantar erythrodysaesthesia syndrome (PT, AEs). There is an indication of lesser harm of selpercatinib in comparison with cabozantinib or vandetanib.

A statistically significant difference to the disadvantage of selpercatinib was shown for each of the outcomes dry mouth (PT, AEs) and alanine aminotransferase increased (PT, severe AEs). There is a hint of greater harm of selpercatinib in comparison with cabozantinib or vandetanib.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for this assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The company did not present separate Kaplan-Meier curves for the subgroup analyses in Module 4 B.

The results are presented in Table 16.

Table 16: Subgroups (morbidity, health-related quality of life, time to event) – RCT, direct comparison: selpercatinib vs. cabozantinib or vandetanib

Study Outcome category Outcome	selpercatinib		cabozantinib or vandetanib		selpercatinib vs. cabozantinib or vandetanib	
Characteristic Subgroup	N	Median time to event in months [95 % CI] Patients with event n (%)	N	Median time to event in months [95 % CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
LIBRETTO-531						
Health-related quality of life						
Physical functioning (EORTCT QLQ-C30 – time to 1st deterioration[c])						
Age						
< 65 years	144	37.2 [27.63; NC] 56 (38.9)	72	2.8 [1.84; 5.55] 45 (62.5)	0.30 [0.20; 0.45]	< 0.001
≥ 65 years	49	4.6 [2.76; 11.76] 31 (63.3)	26	2.1 [1.05; 8.54] 16 (61.5)	0.63 [0.35; 1.16]	0.140
Total					Interaction:	0.038

a. HR from unstratified Cox model with treatment as a covariable.
b. Unstratified log-rank test.
c. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial

Morbidity

Health-related quality of life (EORTC QLQ-C30)

Physical functioning

An effect modification for the characteristic age was found for the physical functioning scale of the EORTC QLQ-C30.

For patients < 65 years of age, a statistically significant difference was shown in favour of selpercatinib in comparison with cabozantinib or vandetanib. For this patient group there is a hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib.

No statistically significant difference was shown between the treatment arms for patients ≥ 65 years. There is no hint of an added benefit of selpercatinib in comparison with cabozantinib or vandetanib for this patient group; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier did not provide any details as to whether the following outcomes on symptoms and side effects were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, insomnia, appetite loss, and diarrhoea)

For the EORTC QLQ-C30 scales fatigue, nausea and vomiting, pain, insomnia, appetite loss and diarrhoea, insufficient information was available to allow a severity category classification of serious or severe. These outcomes were therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Pain (Worst Pain NRS)

No information was available on the patients' scores at the start of or during the study. There was also no information on patients' scores after pain progression. For the outcome pain (Worst Pain NRS), there was therefore insufficient information available to allow a severity category classification of serious or severe. These outcomes were therefore assigned to the outcome category non-serious/non-severe symptoms/late complications.

Health status (EQ-5D VAS)

For the outcome health status (EQ-5D VAS), insufficient information was available to allow a severity category classification of serious or severe. These outcomes were therefore assigned to the outcome category non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, the dossier did not contain any information on the severity of the events that occurred. The outcome of discontinuation due to AEs was therefore assigned to the outcome category non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**selpercatinib vs. cabozantinib or vandetanib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.28 [0.12; 0.61]; p < 0.001 Probability: indication	Outcome category: mortality CI_u < 0.85 Added benefit, extent: major
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to 1st deterioration)		
Fatigue	4.6 vs. 1.2 HR: 0.56 [0.41; 0.76]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Nausea and vomiting	19.4 vs. 2.2 HR: 0.44 [0.32; 0.62]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Pain	5.7 vs. 1.9 HR: 0.54 [0.39; 0.74]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Dyspnoea	27.4 vs. 10.6 HR: 0.79 [0.55; 1.13]; p = 0.195	Lesser benefit not proven / added benefit not proven
Insomnia	NA vs. 2.8 HR: 0.55 [0.39; 0.79]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Appetite loss	35.9 vs. 2.0 HR: 0.28 [0.20; 0.39]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable

Table 17: Extent of added benefit at outcome level: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**selpercatinib vs. cabozantinib or vandetanib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Constipation	2.9 vs. 3.7 HR: 1.04 [0.75; 1.45] p = 0.795	Lesser benefit not proven / added benefit not proven
Diarrhoea	NA vs. 2.0 HR: 0.39 [0.28; 0.55]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Pain (Worst Pain NRS) – time to 1st deterioration	NA vs. 9.1 HR: 0.42 [0.27; 0.65]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Health status (EQ-5D VAS, time to 1st deterioration)	38.7 vs. 3.7 HR: 0.40 [0.28; 0.58]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Health-related quality of life		
EORTC QLQ-C30 – time to 1st deterioration		
Global health status	5.4 vs. 1.8 HR: 0.53 [0.39; 0.72]; p < 0.001 Probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Added benefit, extent: major
Physical functioning Age		
< 65 years	37.2 vs. 2.8 HR: 0.30 [0.20; 0.45] p < 0.001 Probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Added benefit, extent: major
≥ 65 years	4.6 vs. 2.1 0.63 [0.35; 1.16] p = 0.140	Lesser benefit not proven / added benefit not proven
Role functioning	5.8 vs. 1.9 HR: 0.49 [0.36; 0.66]; p < 0.001 Probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Added benefit, extent: major
Emotional functioning	29.1 vs. 5.2 HR: 0.51 [0.35; 0.74]; p < 0.001 Probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Added benefit, extent: major

Table 17: Extent of added benefit at outcome level: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**selpercatinib vs. cabozantinib or vandetanib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Cognitive functioning	5.6 vs. 4.4 HR: 0.73 [0.53; 0.99]; p = 0.046 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent minor
Social functioning	9.0 vs. 2.2 HR: 0.53 [0.38; 0.72]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: major
Side effects		
SAEs	NA vs. 30.3 HR: 0.59 [0.38; 0.92]; p < 0.017 Probability: hint	Outcome category: serious/severe side effects $0.90 < CI_u < 1.00$ Lesser harm, extent: minor
Severe AEs	10.1 vs. 1.9 HR: 0.54 [0.40; 0.73]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm, extent: major
Discontinuation due to AEs	NA vs. NA HR: 0.11 [0.05; 0.23]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser harm, extent: considerable
PRO-CTCAE	No suitable data	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	2.3 vs. 0.5 HR: 0.53 [0.40; 0.71] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser harm, extent: considerable
Dry mouth (AEs)	NA vs. NA HR: 3.65 [1.88; 7.09]; HR: 0.27 [0.14; 0.53][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Greater harm, extent: considerable
Diarrhoea (AEs)	NA vs. 3.0 HR: 0.27 [0.19; 0.40]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser harm, extent: considerable
Nausea (AEs)	NA vs. NA HR: 0.22 [0.12; 0.38]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Lesser harm, extent: considerable

Table 17: Extent of added benefit at outcome level: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**selpercatinib vs. cabozantinib or vandetanib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Vomiting (AEs)	NA vs. 40.0 HR: 0.26 [0.14; 0.47]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: considerable
Stomatitis (AEs)	NA vs. NA HR: 0.14 [0.06; 0.33]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: considerable
Asthenia (AEs)	NA vs. NA HR: 0.37 [0.21; 0.63]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: considerable
Mucosal inflammation (AEs)	NA vs. NA HR: 0.23 [0.12; 0.45]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: considerable
Skin and subcutaneous tissue disorders (AEs)	NA vs. 1.0 HR: 0.27 [0.20; 0.37]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: considerable
Palmar-plantar erythrodysaesthesia syndrome (AEs)	NA vs. NA HR: 0.06 [0.03; 0.13]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Lesser harm, extent: considerable
Alanine aminotransferase increased (severe AEs)	NA vs. NA HR: 5.16 [1.21; 22.07]; HR: 0.19 [0.05; 0.83][c]; p = 0.014 Probability: hint	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 Greater harm, extent: considerable
Metabolism and nutrition disorders (severe AEs)	NA vs. NA HR: 0.19 [0.09; 0.41]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: major
Nervous system disorders (severe AEs)	NA vs. NA HR: 0.29 [0.09; 0.93]; p = 0.027 Probability: hint	Outcome category: serious/severe side effects 0.90 < CI_u < 1.00 Lesser harm, extent: minor
Blood and lymphatic system disorders (severe AEs)	NA vs. NA HR: 0.17 [0.05; 0.60]; p = 0.002 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: major

Table 17: Extent of added benefit at outcome level: selpercatinib vs. cabozantinib or vandetanib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**selpercatinib vs. cabozantinib or vandetanib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Respiratory, thoracic and mediastinal disorders (severe AEs)	NA vs. NA HR: 0.17 [0.04; 0.74]; p = 0.008 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: major

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NRS: numeric rating scale; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of selpercatinib in comparison with cabozantinib or vandetanib (multipage table)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: indication of an added benefit – extent: major	–
Outcomes with shortened observation period	
Morbidity ▪ Symptoms (EORTC QLQ-C30) ▫ Fatigue: hint of an added benefit – extent: considerable ▫ Nausea and vomiting: hint of an added benefit – extent: considerable ▫ Pain: hint of an added benefit – extent: considerable ▫ Insomnia: hint of an added benefit – extent: considerable ▫ Appetite loss: hint of an added benefit – extent: considerable ▫ Diarrhoea: hint of an added benefit – extent: considerable ▪ Pain (Worst Pain NRS): hint of an added benefit – extent: considerable ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: considerable	–

Table 18: Positive and negative effects from the assessment of selpercatinib in comparison with cabozantinib or vandetanib (multipage table)

Positive effects	**Negative effects**
Health-related quality of life (EORTC QLQ-C30) ▪ Global health status: hint of an added benefit – extent: major ▪ Physical functioning ▫ Age < 65 years Hint of an added benefit – extent: major ▪ Role functioning: hint of an added benefit – extent: major ▪ Emotional functioning: hint of an added benefit – extent: major ▪ Cognitive functioning: hint of an added benefit – extent: minor ▪ Social functioning: hint of an added benefit – extent: major	–
Serious/severe side effects ▪ Severe AEs: hint of lesser harm – extent: major ▫ Metabolism and nutrition disorders (severe AEs): hint of lesser harm – extent: major ▫ Nervous system disorders (severe AEs): hint of lesser harm – extent: minor ▫ Blood and lymphatic system disorders (severe AEs): hint of lesser harm – extent: major ▫ Respiratory, thoracic and mediastinal disorders (severe AEs): hint of lesser harm – extent: major ▪ SAEs: hint of lesser harm – extent: minor	Serious/severe side effects ▪ Severe AEs ▫ Alanine aminotransferase increased (severe AEs): hint of greater harm – extent: considerable
Non-serious/non-severe symptoms/late complications ▪ Discontinuation due to AEs: hint of lesser harm – extent: considerable ▪ Gastrointestinal disorders, diarrhoea (AEs), nausea (AEs), vomiting (AEs), asthenia (AEs), skin and subcutaneous tissue disorders (AEs): hint of lesser harm – extent: considerable ▪ Stomatitis (AEs), mucosal inflammation (AEs), palmar-plantar erythrodysaesthesia syndrome (AEs): indication of lesser harm – extent: considerable	Non-serious/non-severe symptoms/late complications ▪ Dry mouth (AEs): hint of greater harm – extent: considerable
No suitable data were available for PRO-CTCAE.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; NRS: numeric rating scale; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale	

Overall, the positive effects of selpercatinib clearly outweigh those of the ACT in all outcome categories in patients with advanced RET-mutant MTC.

In particular, there is an indication of a major added benefit for the outcome overall survival, and consistent positive effects for the majority of scales used to record health-related quality of life, with hints of an added benefit of major extent. In addition, there are positive effects on patient-reported symptoms.

The positive effects also predominate when considering the outcomes in the side effects category, particularly with a hint of lesser harm of major extent in the overall rate of severe AEs.

In contrast, there are isolated negative effects for specific AEs, which, however, do not call into question the major extent of the added benefit.

The result of the assessment of the added benefit of selpercatinib in comparison with the ACT is summarized in Table 19.

Table 19: Selpercatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents 12 years and older with advanced RET-mutant MTC; first-line therapy	vandetanib or cabozantinib[b]	Indication of major added benefit[c, d]

a. Presented is the ACT specified by the G-BA.
b. When determining the ACTs, according to the G-BA, it is assumed that curative treatment measures and local treatment options are no longer considered. It is also assumed, according to the G-BA, that, based on their symptoms, patients are indicated for systemic antineoplastic therapy and therefore a 'watch and wait' strategy, among others, is not an option.
c. Patients with an ECOG PS of 0 to 2 were included in LIBRETTO-531. However, the number of patients with ECOG PS 2 was a maximum of 5, so it remains unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.
d. Only one patient under the age of 18 was included in LIBRETTO-531. It remains unclear whether the observed effects can be transferred to patients under 18 years.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer; RET: rearranged during transfection

The assessment described above concurs with that by the company.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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