IQWiG Reports – Commission No. A22-106

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

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Selpercatinib (RET-mutiertes medulläres Schilddrüsenkarzinom, Erstlinie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present 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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MTC	medullary thyroid cancer
MTD	maximum tolerable dose
PFS	progression-free survival
RCT	randomized controlled trial
RET	rearranged during transfection
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) 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 4 October 2022.

Research question

The aim of the present report was to assess the added benefit of selpercatinib in comparison 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). Subject matter of the present benefit assessment are patients in the first-line setting. The benefit 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 assessed (see dossier assessment A21-28 as well as the decision and justification by the G-BA) and was not subject of the present benefit assessment.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of selpercatinib

Therapeutic indication	**ACT[a]**
Adults and adolescents aged 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. The determination of the ACTs was based on the assumption that curative treatment measures and local treatment options were no longer indicated. In accordance with the G-BA, patients were likewise assumed to be indicated for systemic antineoplastic therapy based on their symptoms, and therefore, a "watch & wait" strategy, for instance, would be inappropriate.

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

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

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

Results

Concurring with the company, the check of completeness of the study pool identified no randomized controlled trials (RCTs) for a direct comparison of selpercatinib versus the ACT or for an adjusted indirect comparison via a common comparator. While the potentially relevant RCT LIBRETTO-531 enrolling patients with locally advanced or metastatic RET-mutant MTC

without prior kinase inhibitor therapy was identified for the comparison of selpercatinib versus cabozantinib or vandetanib, results of this ongoing study are not yet available.

Since the company found no RCTs suitable for direct comparisons or adjusted indirect comparisons, it additionally conducted an information retrieval for other investigations and, alongside an uncontrolled study on the intervention side, presented a comparison of individual arms from different studies.

Evidence presented by the company on selpercatinib – LIBRETTO-001 study

LIBRETTO-001 is an ongoing, uncontrolled, prospective basket study organized into 2 phases. The completed phase 1 determined the maximum tolerable dose (MTD). In the ongoing phase 2, MTD was applied in several patient cohorts. These 2 phases have already been described in detail in dossier assessment A21-28.

For the present therapeutic indication, adults and adolescents aged 12 years and older with advanced RET-mutant MTC who have not received any prior systemic therapy are relevant. However, the subpopulation submitted by the company includes patients who had already received systemic prior therapy (19.0%).

The data submitted by the company additionally comprise patients from both phase 1 and phase 2 of the study. In this regard, the company reports that, like in the LIBRETTO-001 study and the regulatory analyses, no restrictions were applied with regard to the initial dose of selpercatinib. Among the patients in the subpopulation submitted by the company, 13.4% received an initial dose departing from the recommendations of the Summary of Product Characteristics (SPC).

In Module 4 B, the company presented results from the LIBRETTO-001 study. From the company's point of view, intraindividual changes in the course of treatment with selpercatinib show a reduction in symptom burden (particularly diarrhoea, pain, and fatigue) and an improvement in quality of life compared to baseline. Additionally, the company claims high rates of overall survival and progression-free survival (PFS) as well as high rates of patients with an objective tumour response.

Evidence presented by the company for the ACT

For its planned comparisons of individual arms from different studies, the company identified the studies EXAM, Koehler 2022, Study 104, Study 008, and Valerio 2020 on the comparator side. The EXAM study is an RCT comparing cabozantinib versus placebo, while the remaining 4 studies are uncontrolled studies on cabozantinib and/or vandetanib. The company obtained the data presented in the dossier from the respective publications of the studies and additionally from publicly accessible information in dossiers for the EXAM study, Study 104, and Study 008, which have already been reviewed as part of benefit assessments of cabozantinib or vandetanib. The company also found 5 further studies on the ACT; however, it decided to exclude them from comparisons because (a) they failed to separately present patients with RET-

mutant MTC, (b) data were available only for a small number of RET-mutant patients, (c) only children and adolescents were included, or (d) the dosage deviated from approval.

Comparisons of individual arms from different studies

For the comparison of selpercatinib versus the ACT in the subpopulation used by the company, the latter presented results from the 4th data cut-off (15 June 2021) on the outcomes of overall survival, PFS, tumour response, and outcomes from the side effects category, comparing them to the results found in the 5 studies in its study pool on the comparator side. Depending on the availability of data regarding the above individual outcomes, the company considered the following studies on the comparator side:

- overall survival: Koehler 2022 (vandetanib/cabozantinib)
- PFS: EXAM (cabozantinib), Koehler 2022 (vandetanib/cabozantinib), Study 104 (vandetanib), Valerio 2020 (vandetanib)
- tumour response : Koehler 2022 (vandetanib/cabozantinib), Study 008 (vandetanib), Study 104 (vandetanib)
- side effects: EXAM (cabozantinib), Koehler 2022 (vandetanib/cabozantinib), Study 008 (vandetanib), Study 104 (vandetanib), Valerio 2020 (vandetanib)

The company presented separate indirect comparisons of the LIBRETTO-001 study with each of the individual arms from the different studies on the comparator side. For this purpose, it presented both unweighted comparisons and matching-adjusted indirect comparison (MAIC) analyses. For the outcomes of overall survival, PFS, and for individual categories of tumour response, the respective sources supplied Kaplan-Meier curves which were used to generate data for time-to-event analyses. For other categories of tumour response and for the outcomes of the side effects category, the company calculated approximate relative risks using 95% confidence intervals.

Overall, the company claimed a hint of non-quantifiable, but at least minor, added benefit for selpercatinib based on an overall consideration of the available evidence (comparisons of individual arms from different studies as well as the LIBRETTO-001 study).

Assessment of the evidence presented by the company

The data presented by the company in Module 4 B are unsuitable for assessing the benefit of selpercatinib versus the ACT. This is explained below.

Uncontrolled LIBRETTO-001 study permits no conclusions on added benefit

The company presented the results of the uncontrolled LIBRETTO-001 study and conducted descriptive analyses of the results. Since they do not allow a comparison with the ACT, the results from the LIBRETTO-001 study alone are unsuitable for assessing the added benefit of selpercatinib versus the ACT.

Comparisons presented by the company are unsuitable for drawing conclusions on added benefit

The comparisons of individual arms from different studies presented by the company are unsuitable for drawing conclusions on added benefit. The rationale is provided below.

Patient populations not comparable

The studies on the intervention and comparator side are not comparable with regard to the included patients. In particular, differences are found in the course of disease. For example, the patient population of the LIBRETTO-001 study and the populations of the comparator therapy studies differ with regard to the interval between the diagnosis of disease and start of treatment with selpercatinib or the comparator therapy. In comparison with the Koehler 2022 and Valerio 2020 studies, the interval between initial diagnosis and treatment start was much longer in the LIBRETTO-001 study. Information on the interval between initial diagnosis and treatment start is missing for Study 104, which provides information only on the interval between diagnosis of a locally advanced or metastatic MTC and the 1st dose of vandetanib. However, the time since metastatic diagnosis was much longer in the LIBRETTO-001 study than in Study 104. Only Study 008 had a longer interval between initial diagnosis and treatment start than the LIBRETTO-001 study.

In addition, patient populations potentially differ in terms of disease stages. The information in the study report indicates that about 35% of patients in the LIBRETTO-001 study's subpopulation used by the company were in stage IVC. Hence, these patients had distant metastases at the time of study inclusion. However, 12% of patients were in the less advanced disease stages IVA and IVB. For 47% of patients, the data show only stage IV, without further differentiating between stages IVA to IVC; overall, it therefore remains unclear how many of the patients in the subpopulation submitted by the company were in stage IVC. In the studies on the comparator side, by contrast, the vast majority of patients were in stage IVC.

Additionally, the therapeutic indications of selpercatinib and vandetanib differ. According to the SPC, the use of vandetanib is restricted to the treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced, or metastatic disease. According to the selpercatinib SPC, its use is not restricted to aggressive disease. Based on the available information, it is impossible to conclusively determine whether vandetanib was used in line with approval in the studies on the comparator side. However, the shorter interval between initial diagnosis and treatment start as well as the high percentage of patients in disease stage IVC suggest that, unlike the LIBRETTO-001 study, the studies on the comparator side enrolled patients who were in a more advanced disease stage and/or had a more aggressive disease course. These differences in the patient populations therefore correspond to the above-mentioned differences in the therapeutic indication.

For the comparisons of individual arms from different studies regarding the outcome of overall survival, the company used only the Koehler 2022 study on the comparator side. In addition to the above points, the comparability of the patient populations for this comparison is limited by

the fact that the Koehler 2022 study enrolled patients who were initially diagnosed in 1990 and later, while recruitment for the LIBRETTO-001 study started only in 2017. Therefore, the 2 studies may potentially differ substantially in terms of their healthcare context.

Furthermore, some other aspects of the individual studies call into question the comparability of the patient population.

In summary, the patient populations on the 2 sides of the comparisons of individual arms from different studies are not comparable with regard to the course of disease and/or aggressiveness of disease. As a result, it remains unclear whether the advantages of selpercatinib in comparison with the ACT as described by the company are due to selpercatinib treatment or to differences in the patient populations, particularly to more advanced and/or more aggressive disease in the studies on the comparator side.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of selpercatinib in comparison with the ACT; an added benefit is therefore not proven.

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

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 aged 12 years and older with advanced RET-mutant MTC; first-line therapy	Vandetanib or cabozantinib[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The ACTs were determined based on the assumption that curative treatment measures and local treatment options were no longer indicated. In accordance with the G-BA, patients were likewise assumed to be indicated for systemic antineoplastic therapy based on their symptoms, and therefore, a "watch & wait" strategy, for instance, would be inappropriate.

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

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report was to assess the added benefit of selpercatinib in comparison with vandetanib or cabozantinib as the ACT in adults and adolescents aged 12 years and older with advanced RET-mutant MTC. Subject matter of the present benefit assessment are patients in the first-line setting. The benefit of selpercatinib in adults and adolescents aged 12 years and older with advanced RET-mutant MTC who require systemic therapy following prior cabozantinib and/or vandetanib treatment has already been assessed (see dossier assessment A21-28 [3] as well as the G-BA's decision [4] and justification [5]) and was not the subject matter of the present benefit assessment.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of selpercatinib

Therapeutic indication	**ACT**[a]
Adults and adolescents aged 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. The ACTs were determined based on the assumption that curative treatment measures and local treatment options were no longer indicated. In accordance with the G-BA, patients were likewise assumed to be indicated for systemic antineoplastic therapy based on their symptoms, and therefore, a "watch & wait" strategy, for instance, would be inappropriate.

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

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

In the wording of its research question, the company departs from the G-BA's specification in that it takes into account adults and adolescents aged 12 years and older with advanced RET-mutant MTC without prior therapy with multikinase inhibitors. The company therefore included not only patients in first-line therapy, but also patients who had already received systemic prior therapy not based on multikinase inhibitors. The present benefit assessment is conducted only for the population specified by the G-BA.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on selpercatinib (status: 15 August 2022)
- bibliographical literature search on selpercatinib (last search on 15 August 2022)
- search in trial registries / trial results databases for studies on selpercatinib (last search on 17 August 2022)
- search on the G-BA website for selpercatinib (last search on 17 August 2022)
- bibliographical literature search on the ACT (last search on 15 August 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 17 August 2022)
- search on the G-BA website for the ACT (last search on 16 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on selpercatinib (last search on 13 October 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool identified no RCTs suitable for a direct comparison of selpercatinib versus the ACT or for an adjusted indirect comparison via a common comparator. While the potentially relevant RCT LIBRETTO-531 [6], which compares patients with locally advanced or metastatic RET-mutant MTC without prior kinase inhibitor therapy, was found for the comparison of selpercatinib versus cabozantinib or vandetanib, results of this ongoing study are not yet available.

Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it additionally conducted an information retrieval for further studies and, alongside an uncontrolled study on the intervention side, presented a comparison of individual arms from different studies.

The completeness of the company’s study pool regarding further investigations for the ACT was not checked. The check of completeness of the company's study pool for other investigations on selpercatinib found 1 additional potentially relevant study (LIBRETTO-321) [7]. The LIBRETTO-321 study enrolled 17 patients with advanced RET-mutant MTC who received selpercatinib in first-line therapy. The company’s assessment disregarded the LIBRETTO-321 study, citing the low number of patients in the relevant subpopulation. However, the company’s submitted subpopulation from the study it included on the intervention side likewise comprises only 142 patients. The company’s exclusion of the LIBRETTO-321 study nevertheless remains without consequence because the data submitted by the company

are overall unsuitable for drawing any conclusions on the added benefit of selpercatinib in comparison with the ACT. The reasons are explained below.

I 3.1 Evidence provided by the company

For selpercatinib, the company included the uncontrolled basket study LIBRETTO-001 [8,9], analysing the subpopulation of patients with advanced RET-mutant MTC.

Moreover, the company used comparisons of individual arms from different studies. For these comparisons, the company identified 5 studies on the comparator side, including 1 RCT (EXAM) [10-12] and 4 uncontrolled studies (Koehler 2022 [13], Study 104 [14], Study 008 [15,16], and Valerio 2020 [17]) (for details, see Table 6 in I Appendix B of the full dossier assessment).

I 3.1.1 Evidence on selpercatinib

Study LIBRETTO-001

LIBRETTO-001 is an ongoing, non-controlled, prospective basket study organized in 2 phases. The MTD was determined in the already completed phase 1. In the ongoing phase 2, the MTD was applied in several patient cohorts. The 2 phases have already been described in detail in dossier assessment A21-28 [3].

Data cut-offs and analysis populations

According to the company, 5 data cut-offs are available for the LIBRETTO-001 study:

- data cut-off 1: 17 June 2019 with 531 patients (interim analysis)
- data cut-off 2: 16 December 2019 with 702 patients (interim analysis used as the basis for the initial European approval)
- data cut-off 3: 30 March 2020 with 746 patients (data cut-off requested by the Japanese regulatory authority; confirmatory data cut-off for the initial European approval)
- data cut-off 4: 15 June 2021 with 796 patients (interim analysis used as the basis for the European approval of the indication extension [first-line treatment of advanced RET-mutant MTC])
- data cut-off 5: 24 September 2021 with 45 patients (in consultation with the US regulatory authority; comprises data only from cohorts of RET fusion-positive tumours except NSCLC and thyroid cancer)

The company presents analyses on the 4st data cut-off in Module 4B of the dossier and uses it for the benefit assessment.

For the present therapeutic indication, adults and adolescents aged 12 years and older with advanced RET-mutant MTC who have not received any prior systemic therapy are relevant. The subpopulation submitted by the company, which it refers to as MTCA (142 patients), in

contrast, also includes 27 patients (19.0%) who had already received prior systemic therapy. Ten of these patients had received prior treatment with a multikinase inhibitor.

Furthermore, the data submitted by the company comprise patients from both phase 1 and phase 2 of the study. In this context, the company reports that, like in the LIBRETTO-001 study and the regulatory analyses, no restrictions were applied with regard to the initial dose of selpercatinib. Among the 142 patients in the subpopulation submitted by the company, 19 patients (13.4%) received an initial dose departing from the recommendations of the SPC [18]. In addition, the subpopulation submitted by the company exhibits further deviations from the SPC. For example, the dose was reduced to 60 mg in 15 patients, and 15 patients were treated beyond disease progression.

Analogous to dossier assessment A21-28, the company's dossier distinguishes between 2 analysis populations, the safety analysis set and the efficacy analysis set. The analyses on adverse events were based on the safety analysis set, which includes all patients who had received at least 1 dose of selpercatinib. The analyses of the benefit outcomes were based on the efficacy analysis set, which includes only patients who had either received the 1st dose of selpercatinib at least 6 months before the data cut-off or whose treatment had been discontinued within 6 months after the start of therapy. At the time of the 4th data cut-off, on which the analyses presented by the company are based, these 2 analysis sets were identical for the subpopulation submitted by the company.

Presented results

In Module 4B, the company presented results from the LIBRETTO-001 study. From the company's point of view, intraindividual changes in the course of treatment with selpercatinib show a reduction in symptom burden (particularly diarrhoea, pain, and fatigue) and an improvement in quality of life compared to baseline. In addition, the company claims high rates of overall survival and PFS as well as high rates of patients with an objective tumour response are shown.

I 3.1.2 Evidence on the ACT

On the comparator side, the company identified the studies EXAM, Koehler 2022, Study 104, Study 008, and Valerio 2020 for its envisaged comparisons of individual arms from different studies (see Table 6 in I Appendix B of the full dossier assessment). The EXAM study is an RCT comparing cabozantinib versus placebo, while the remaining 4 studies are uncontrolled studies on cabozantinib and/or vandetanib. The company obtained the data presented in the dossier from the respective publications on the studies and – for the EXAM study, Study 104 and Study 008, which were already the subject matter of benefit assessments of cabozantinib or vandetanib – from their dossiers' publicly accessible information [19,20]. The company also found 5 other studies on the ACT [21-25] but disregarded them in its comparison because according to the company, (a) they did not provide a differentiated presentation for patients

with RET-mutant MTC, (b) data are available only for a small number of RET-mutant patients, (c) only children and adolescents were included, or (d) the dosage deviated from approval.

EXAM

The EXAM study is a double-blind, international, multicentre RCT comparing cabozantinib versus placebo. The study included patients aged ≥ 18 years with unresectable, locally advanced, or metastatic MTC. Overall, 330 patients were included in the study and randomly allocated in a 2:1 ratio either to treatment with cabozantinib (N = 219) or to placebo (N = 111). For its comparisons on PFS and outcomes in the side effects category, the company takes into account the subpopulation of the 107 patients with confirmed positive RET mutation status who were treated with cabozantinib. Among the 107 patients, 23 (21.5%) had received prior tyrosine kinase inhibitor treatment. No information is available on time since initial diagnosis of disease. Further, no separate information on disease stage is available for the subpopulation of patients with RET-positive tumours. However, the dossier for the early benefit assessment of cabozantinib [19] shows that 96% of the 219 patients in the study's cabozantinib arm were in disease stage IVC. The median treatment duration for the patients in the presented subpopulation was 14 months. The study's primary outcome was PFS; the secondary outcomes comprised overall survival, objective response rate as well as outcomes of the morbidity, health-related quality of life, and side effects categories.

Koehler 2022

In the Koehler 2022 study, registry data of adult patients from 4 German centres were retrospectively analysed; these patients had been diagnosed with locally advanced or metastatic MTC between 1990 and 2019. For its comparisons regarding overall survival, PFS, tumour response and outcomes of the side effects category, the company uses the subpopulation of 36 patients with positive RET mutation status who received first-line vandetanib (N = 33) or cabozantinib (N = 3) treatment. The median interval between initial diagnosis and start of treatment with vandetanib or cabozantinib was 36 months. A total of 34 patients (97%) of the presented subpopulation exhibited distant metastases at the time of treatment start. The median duration of vandetanib or cabozantinib treatment was 21 months. The study objective was to predict the clinical course on multikinase inhibitor treatment in patients with RET-positive MTC.

Study 104

Study 104 is a noninterventional observational study of adult patients treated with vandetanib who have symptomatic, aggressive, locally advanced, or metastatic MTC. The study was conducted as a post-authorization safety study to meet the requirements associated with the conditional approval of vandetanib. The study enrolled patients prospectively and retrospectively (only RET-negative patients). In addition, it enrolled vandetanib-treated patients from the randomized phase-3 study D4200C00058 [23] whose RET mutation status was initially unknown and was retrospectively analysed at enrolment in Study 104. The company took into account results from 55 patients with RET-positive tumours for its comparisons on

PFS, tumour response, and outcomes of the side effects category. For time since initial diagnosis, no information is available for these patients, but the median interval between diagnosis of sporadic, unresectable, locally advanced or metastatic MTC and the start of vandetanib treatment was only 6 months. Of the patients taken into account by the company, 46 (84%) were in disease stage IVC. No information is available on treatment duration. The objective of the study was to assess the benefit-risk ratio for vandetanib in the routine care of RET-positive and RET-negative patients with symptomatic, aggressive, locally advanced, or metastatic MTC.

Study 008

Study 008 is an uncontrolled, multicentre phase-2 study on vandetanib treatment. The study included 30 adult patients with locally advanced or metastatic hereditary MTC and evidence of RET germline mutation who received vandetanib treatment. The company used these 30 patients for comparisons on tumour response and side effects. The information provided by the company in Module 4B shows that up to 15 of the 30 patients might potentially have received prior systemic therapy. On average, the patients were initially diagnosed 16 years ago. The available documents do not show patients' disease stages at study start. Their median duration of vandetanib treatment was 19 months. Primary outcome was objective response rate; other secondary outcomes were outcomes of the morbidity, health-related quality of life, and side effects categories.

Valerio 2020

The Valerio 2020 study is a single-arm observational study enrolling patients who received vandetanib at 1 centre in Italy, either in the context of clinical trials or after marketing authorization. The study enrolled 79 adult patients with locally advanced or metastatic MTC, and the company used them for comparisons on PFS and side effects. A total of 67 patients (85%) had a positive RET mutation status. A publication on the study reports that up to 29 patients (37%) might have potentially received prior systemic therapy [17]. On average, the time from diagnosis of disease to treatment start was 5.4 years. A total of 70 patients (89%) were in disease stage IVC at baseline. While 25 patients (32%) were treated with vandetanib for < 12 months, 54 patients (68%) received vandetanib for ≥ 12 months. The objective of the study was to identify predictive factors for a longer, durable response to vandetanib treatment.

I 3.1.3 Comparisons of individual arms from different studies

For the comparison of selpercatinib versus the ACT for its subpopulation MTC A, the company used the results from the 4th data cut-off (15 June 2021) on the outcomes of overall survival, PFS, tumour response, and outcomes of the side effects category, comparing them to the results found in each of the 5 studies in its study pool. Depending on the availability of data regarding the above individual outcomes, the company considered the following studies on the comparator side:

- overall survival: Koehler 2022 (vandetanib/cabozantinib)

- PFS: EXAM (cabozantinib), Koehler 2022 (vandetanib/cabozantinib), Study 104 (vandetanib), Valerio 2020 (vandetanib)
- tumour response: Koehler 2022 (vandetanib/cabozantinib), Study 008 (vandetanib), Study 104 (vandetanib)
- side effects: EXAM (cabozantinib), Koehler 2022 (vandetanib/cabozantinib), Study 008 (vandetanib), Study 104 (vandetanib), Valerio 2020 (vandetanib)

The company presented separate indirect comparisons of the LIBRETTO-001 study with each of the individual arms from the different studies on the comparator side. For this purpose, it submitted both unweighted comparisons and MAIC analyses. For the outcomes of overall survival, PFS, and for individual categories of tumour response, the respective sources supplied Kaplan-Meier curves, which were used to generate data for time-to-event analyses. For other categories of tumour response and for the outcomes of the side effects category, the company calculated approximate relative risks using 95% confidence intervals.

Overall, the company claimed a hint of non-quantifiable, but at least minor, added benefit for selpercatinib based on an overall consideration of the available evidence (comparisons of individual arms from different studies as well as the LIBRETTO-001 study).

I 3.2 Assessment of the evidence presented by the company

The data presented by the company in Module 4B are unsuitable for assessing the benefit of selpercatinib versus the ACT. The rationale is provided below.

Uncontrolled LIBRETTO-001 study permits no conclusions on added benefit

The company presented the results of the non-controlled LIBRETTO-001 study and performed descriptive considerations of the results. Taken alone, the results from the LIBRETTO-001 study are unsuitable for assessing the added benefit of selpercatinib versus the ACT as they do not allow a comparison with the ACT.

Comparisons presented by the company are unsuitable for drawing conclusions on added benefit

As described in Section I.12, the company analysed results on the outcomes of overall survival, PFS, tumour response, and side effects from different studies for the comparison of selpercatinib versus the ACT in adult patients with advanced RET-mutant MTC without prior systemic therapy (first-line). The comparisons of individual arms from different studies presented by the company are unsuitable for drawing conclusions on added benefit. The rationale is provided below.

Patient populations not comparable

The studies on the intervention and comparator side are not comparable with regard to the included patients. In particular, differences are found in the course of disease. For example, regarding the time interval between diagnosis of disease and start of treatment with

selpercatinib or the comparator therapy, there are marked differences between the patient population picked by the company from the LIBRETTO-001 study and those from the comparator therapy studies (see Table 6 in I Appendix B of the full dossier assessment). The interval between initial diagnosis and treatment start was much longer in the LIBRETTO-001 study (median of 54 months) than in the Koehler 2022 study (median of 36 months). The Valerio 2020 study exhibited a shorter interval as well, albeit in this case, only the means can be compared (65 months versus 104 months in the LIBRETTO-001 study). Information on the interval between initial diagnosis and treatment start is missing for Study 104, where only time since diagnosis of a locally advanced or metastatic MTC and the 1st dose of vandetanib (median of 6 months) is known. However, the time since metastatic diagnosis was much longer in the LIBRETTO-001 study than in Study 104, at a median of 43 months. Only Study 008 (mean of 192 months) had a longer interval between initial diagnosis and treatment start than the LIBRETTO-001 study.

In addition, the patient populations potentially differ in terms of disease stages. The information in the study report indicates that about 35% of patients in the LIBRETTO-001 study's subpopulation used by the company were in stage IVC. Hence, these patients had distant metastases at the time of study inclusion. However, 12% of patients were in the less advanced disease stages IVA and IVB. For 47% of patients, the data show only stage IV, without further differentiating between stages IVA to IVC; overall, it therefore remains unclear how many of the patients in the subpopulation submitted by the company were in stage IVC. In the studies on the comparator side, in contrast, the vast majority of patients were in stage IVC. For example, 97% of Koehler 2022 participants had distant metastases at the start of vandetanib or cabozantinib treatment.

Additionally, the therapeutic indications of selpercatinib and vandetanib differ. According to the SPC, the use of vandetanib is restricted to the treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced, or metastatic disease [26]. According to the vandetanib assessment report by the European Medicines Agency [27], the application of vandetanib requires not only determining whether the disease is symptomatic or progressive, but also taking into account additional biomarkers suggesting an aggressive course of disease (e.g. calcitonin / carcinoembryonic antigen). According to the selpercatinib SPC, its use is not restricted to aggressive disease [18]. On the basis of the available information, it is impossible to conclusively determine whether vandetanib was used in line with approval in the studies on the comparator side, but the shorter interval between initial diagnosis and treatment start as well as the high percentage of patients in disease stage IVC suggest that unlike the LIBRETTO-001 study, the studies on the comparator side enrolled patients in a more advanced disease stage and/or more aggressive course of disease. These differences in the patient populations therefore correspond to the above-mentioned differences in the therapeutic indication.

For the comparisons of individual arms from different studies regarding the outcome of overall survival, the company used only the Koehler 2022 study on the comparator side. In addition to the above points, the comparability of the patient populations for this comparison is limited by

the fact that the Koehler 2022 study enrolled patients who were initially diagnosed in 1990 and later, while recruitment for the LIBRETTO-001 study started only in 2017. Therefore, the 2 studies may potentially differ substantially in terms of their healthcare context.

Furthermore, some additional aspects of the individual studies call into question the comparability of the patient populations:

- Radiographic evidence of tumour progression was an inclusion criterion for Cohort 4 of the LIBRETTO-001 study (patients with advanced RET-mutant MTC without prior therapy with cabozantinib or vandetanib or other kinase inhibitors with anti-RET activity), but this was not the case for all studies on the comparator side. For instance, patients were enrolled in the Koehler 2022 study, Study 104, and Study 008 irrespective of evidence of disease progression.
- The patients with positive RET-mutation status in the EXAM study's cabozantinib arm and the LIBRETTO-001 study's subpopulation presented by the company differ in tumour burden. In the EXAM participants, the median tumour burden (defined as the sum of the longest diameters as assessed by an independent radiological committee) was 111.7 mm (10.7 mm to 420.2 mm) versus 58.6 mm (10.0 mm bis 270.0 mm) in the LIBRETTO-001 study (defined as the sum of the diameters of all target lesions as assessed by the investigator).
- Study 008 included only patients with hereditary MTC and RET germline mutation. The information provided by the company does not show how many patients in the LIBRETTO-001 subpopulation presented by the company had hereditary MTC; it can however be presumed, that this was the case for only some of the participants.

In summary, the patient populations on either side of the comparison of individual arms from different studies are not comparable with regard to the course of disease and/or aggressiveness of disease. As a result, it remains unclear whether the advantages of selpercatinib in comparison with the ACT as described by the company are due to selpercatinib treatment or to differences in the patient populations, particularly to more advanced and/or more aggressive disease in the studies on the comparator side.

Additional points of criticism on the comparisons presented by the company

Irrespective of the fact that the analyses presented by the company are unsuitable for the benefit assessment on the grounds of the patient populations in the studies not being comparable on the intervention and comparator sides, the following additional points of criticism apply to the analyses presented by the company:

- In its analyses on outcomes of the side effects category, the company compares the percentages of patients with event and calculates the approximate relative risks using 95% confidence intervals. However, such comparisons cannot be interpreted if (a) the treatment durations of the LIBRETTO-001 study and the studies on the comparator side

differ markedly (which they do in some cases) or (b) no information is available on the studies' treatment durations (see Table 6 in I Appendix B of the full dossier assessment).

- Except for Koehler 2022, the studies included by the company each comprised some patients who were no longer in first-line therapy in the population used for the company's analyses. For instance, 21.5% of patients with positive RET mutation status in the EXAM study's cabozantinib arm had already received prior treatment with a tyrosine kinase inhibitor. For Study 104, the company's dossier contains no information at all on prior therapies (see Table 6 in I Appendix B of the full dossier assessment).
- MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [1]. In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data [28]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of selpercatinib.

Conclusion

The results presented by the company are unsuitable for an assessment of added benefit of selpercatinib in comparison with the ACT. The results from the uncontrolled study LIBRETTO-001 alone are unsuitable for the benefit assessment because no data are available on the ACT. Moreover, the comparisons of individual arms from different studies presented by the company are unsuitable for drawing any conclusions on added benefit because the patient populations in the studies on the intervention and comparator side are not comparable with regard to the course of disease and/or aggressiveness of disease.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of selpercatinib in comparison with the ACT in adults and adolescents aged 12 years and older with advanced RET-mutant MTC without prior systemic treatment (first line). There is no hint of an added benefit of selpercatinib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for selpercatinib in comparison with the ACT.

Table 5: Selpercatinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults and adolescents aged 12 years and older with advanced RET-mutant MTC; first-line therapy	Vandetanib or cabozantinib[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The ACTs were determined based on the assumption that curative treatment measures and local treatment options were no longer indicated. In accordance with the G-BA, patients were likewise assumed to be indicated for systemic antineoplastic therapy based on their symptoms, and therefore, a "watch & wait" strategy, for instance, would be inappropriate.

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

The assessment described above deviates from the company's assessment, which, on the basis of the 4th data cut-off of the uncontrolled LIBRETTO-001 study and the comparisons of individual arms from different studies, derived a hint of a non-quantifiable, but at least minor, added benefit for its subpopulation MTC A.

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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