IQWiG Reports – Commission No. A21-28

Selpercatinib (RET-mutant medullary thyroid cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Selpercatinib (RET-mutiertes medulläres Schilddrüsenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 June 2021). Please note: This translation 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
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
TKI	tyrosine kinase inhibitor

2 Benefit assessment

2.1 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 15 March 2021.

Research question

The aim of the present report was to assess the added benefit of selpercatinib in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in adults and adolescents aged 12 years and older with advanced rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC) who require systemic therapy following treatment with cabozantinib and/or vandetanib.

The research question presented in Table 2 resulted 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 12 years and older with advanced RET MTC cancer who require systemic therapy following treatment with cabozantinib and/or vandetanib	BSC[b]
a. Presentation of the ACT specified by the G-BA. b. The determination of the ACT was based on the assumption that curative treatment measures were no longer indicated. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer; RET: rearranged during transfection	

The company deviates from the ACT by considering vandetanib and cabozantinib as comparator therapy in addition to BSC. The arguments presented by the company to justify its deviation from the ACT do not indicate that cabozantinib and vandetanib had to be part of the ACT.

The assessment was conducted in comparison with the G-BA's ACT and 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 the completeness of the study pool identified no randomized controlled trials (RCTs) on the direct comparison or on the adjusted indirect comparison using a common comparator of selpercatinib versus BSC.

The company additionally conducted an information retrieval and presented the non-controlled study LIBRETTO-001 on selpercatinib. Moreover, it conducted comparisons of individual arms from different studies using 2 RCTS for BSC, each of which contained a placebo arm with adequate implementation of the BSC (see below).

Evidence on selpercatinib presented by the company

The basket study LIBRETTO-001 is an ongoing, non-controlled, prospective study organized in 2 phases. The maximum tolerable dose (MTD) was determined in the already completed phase 1. In the ongoing phase 2, the MTD was applied.

Phase 1 of the LIBRETTO-001 study

Phase 1 of the LIBRETTO-001 study included patients aged 12 years and older with locally advanced or metastatic solid tumours, regardless of RET status and pretreatment, who had progressed on or were intolerant to previous standard therapies, for whom no standard therapy was available, for whom standard therapy was not indicated from the investigator's point of view, or who refused standard therapy. The presence of an alteration of the RET gene was only an inclusion criterion after the minimum plasma concentration of selpercatinib specified in the study protocol had been reached. Treatment with certain drugs, e.g. cabozantinib and/or vandetanib was allowed, but presented no inclusion criterion.

Aim of phase 1 was the determination of the MTC.

Phase 2 of the LIBRETTO-001 study

In phase 2 of the LIBRETTO-001 study, patients aged 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into 6 different cohorts with the tumour entities comprised in the basket. In the present therapeutic indication, the cohort with advanced MTC with a RET mutation and progression under standard therapy or intolerance to standard therapy is significantly relevant.

For all patients of phase 2, treatment started with 160 mg twice daily in 28-day cycles, irrespective of body weight; this does not correspond to the specifications of the Summary of Product Characteristics (SPC) for patients with a body weight of < 50 kg. Treatment was continued until occurrence of unacceptable toxicity, or occurrence of another event that led to treatment discontinuation (e.g. death, withdrawal of consent). In the event of progression, treatment could be continued in agreement with the company if tolerability and clinical benefit were given.

Primary outcome in phase 2 was the objective response rate. Patient-relevant secondary outcomes were "overall survival", "morbidity", "health-related quality of life" and "side effects".

Evidence presented by the company for the ACT (BSC)

Study EXAM

The EXAM study is a double-blind, international, multicentre RCT on the comparison of cabozantinib with placebo. 330 adult patients with unresectable locally advanced or metastatic MTC who had radiographically diagnosed progression within the last 14 month before study inclusion were randomly assigned to an intervention group (cabozantinib) or a control group (placebo) in a 2:1 ratio. The intention to treat (ITT) population consisted of 219 patients in the intervention group and 111 patients in the control group. Presence of a RET alteration was no inclusion criterion. Therefore, not all patients had RET mutation. In the control group, 62 (56%) patients had RET mutations, of whom 45 (41% of the ITT population) had M918T RET mutations. Of the 111 patients in the control group, 64 (58%) had no prior systemic therapy and 47 (42%) had ≥ 1 prior systemic therapy. 9 (8%) patients were pretreated with vandetanib. Pretreatment with cabozantinib was an exclusion criterion. Primary outcome was progression-free survival (PFS); the secondary outcomes comprised overall survival, objective response rate, morbidity, health-related quality of life and side effects.

Study Wells 2012

Wells 2012 is a double-blind, international, multicentre RCT comparing vandetanib with placebo; however, for the comparison of the results (overall survival and PFS) of the LIBRETTO 001 study with the Wells 2012 study, the company only performed descriptive comparisons, as analyses on patients with RET mutation were lacking.

Assessment of the evidence presented by the company

The non-controlled study LIBRETTO-001 permits no conclusions on the added benefit

Adults and adolescents 12 years and older with advanced RET-mutant MTC who require systemic therapy following treatment with cabozantinib and/or vandetanib are relevant for the present therapeutic indication. The company presented the results of the subpopulation of the LIBRETTO-001 study who met these criteria. This subpopulation comprised 153 patients.

From the company's point of view, the intraindividual changes in the course of the LIBRETTO-001 study showed a reduction in symptom burden and an improvement in quality of life. Moreover, the company pointed out that the majority of patients achieved a better overall response under treatment with selpercatinib than under the treatment provided immediately before study inclusion.

The results from the LIBRETTO-001 study alone are not suitable for the benefit assessment, as they do not permit a comparison with the ACT. The assessment of the added benefit requires comparative data.

Inclusion criteria not met for all patients

In the LIBRETTO-001 study and the studies EXAM and Wells 2012, not all patients fulfilled the inclusion criteria of the present research question. The deviations in the LIBRETTO-001

study relate to dosage and treatment beyond progression. The deviations affect at least 26% of the patients. On the comparator side (studies on BSC), only about 50% of patients in the studies EXAM and Wells 2012 had a RET mutation. Moreover, the proportion of patients in the placebo arm who had been pretreated with cabozantinib or vandetanib was very low.

Comparison of individual arms from different studies not suitable for conclusions on the added benefit

For the comparison of selpercatinib with BSC, the company compared the population of the LIBRETTO-001 study pretreated with cabozantinib and/or vandetanib with the EXAM study for the outcomes "overall survival", "PFS" and "objective response rate". In doing so, it considered different analysis populations (e.g. with and without pretreatment) for the calculation of the effect estimations for overall survival.

For the outcomes on side effects, the company presented descriptive comparisons on the number of patients with at least one event, taking into account all patients in the control arms regardless of their RET mutation status.

The comparison of individual arms from different studies is not suitable for conclusions on the added benefit because:

- the patients on the comparator side (EXAM study) did not meet the inclusion criteria of the research question, in particular, there was no restriction to patients pretreated with vandetanib and/or cabozantinib and largely no comparable operationalization of the RET mutation status
- other than postulated by the company, direction and magnitude of potential biases due to known (in particular pretreatment and RET mutation status) as well as unknown confounders cannot be assessed and furthermore
- there are doubts that the patients in the studies LIBRETTO and EXAM are comparable in their prognosis.

In the present data situation, the effects in overall survival observed in the comparison are altogether not large enough that they could not be explained by bias alone.

No usable results on side effects

The observations on side effects presented by the company on the basis of the proportion of patients with event cannot be interpreted in the present situation, as the treatment and observation duration varied greatly between the studies.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of selpercatinib in comparison with the ACT (BSC). The results from the non-controlled study LIBRETTO-001 alone are not suitable for the benefit assessment, as data on the ACT are not

available. Moreover, the comparisons of individual arms from different studies presented by the company are not suitable for conclusions on the added benefit. Finally, a weighing of benefits and harms would not be possible because the results on side effects are not interpretable.

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

Based on the results presented, probability and extent of the added benefit of the drug selpercatinib in comparison with the ACT are assessed as presented in Table 3:

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 who require systemic therapy following prior treatment with cabozantinib and/or vandetanib	BSC[b]	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. The determination of the ACT was based on the assumption that curative treatment measures were no longer indicated. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

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

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of selpercatinib in comparison with BSC as ACT in adults and adolescents aged 12 years and older with advanced rearranged during RET-mutant MTC who require systemic therapy following treatment with cabozantinib and/or vandetanib.

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

[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].

Table 4: Research question of the benefit assessment of selpercatinib

Therapeutic indication	ACT[a]
Adults and adolescents 12 years and older with advanced RET MTC cancer who require systemic therapy following treatment with cabozantinib and/or vandetanib	BSC[b]

a. Presentation of the ACT specified by the G-BA.
b. The determination of the ACT was based on the assumption that curative treatment measures were no longer indicated. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

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

The company deviates from the ACT by considering vandetanib and cabozantinib as comparator therapy in addition to BSC. The arguments presented by the company to justify its deviation from the ACT do not indicate that cabozantinib and vandetanib had to be part of the ACT.

The assessment was conducted in comparison with the G-BA's ACT and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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: 23 February 2021)
- bibliographical literature search on selpercatinib (last search on 23 February 2021)
- search in trial registries/trial results databases for studies on selpercatinib (last search on 23 February 2021)
- search on the G-BA website for selpercatinib (last search on 24 February 2021)
- bibliographical literature search on the ACT (last search on 23 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 23 February 2021)
- search on the G-BA website for the ACT (last search on 24 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on selpercatinib (last search on 23 March 2021); for search strategies, see Appendix C of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCTs on the direct comparison or on the adjusted indirect comparison of selpercatinib versus the ACT (BSC) using a common comparator.

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

The check of the completeness of the company's study pool identified no additional potentially relevant studies on selpercatinib. The completeness of the study pool on BSC was not checked.

The data presented by the company were unsuitable to draw conclusions on the added benefit of selpercatinib in comparison with BSC. This is justified below.

2.3.2 Evidence provided by the company

For selpercatinib, the company included the non-controlled basket study LIBRETTO-001 [3-7] and used the subpopulation of adult patients with advanced RET-mutant MTC who had been pretreated with cabozantinib and/or vandetanib.

Moreover, the company used comparisons of individual arms from different studies. For these comparisons, the company identified 6 studies under consideration of BSC, vandetanib and cabozantinib. 4 of the studies are non-controlled studies on vandetanib or cabozantinib (3 vandetanib [8-10] and 1 cabozantinib [11]); these studies are not suitable for conclusions on the added benefit as they do not contain data on the ACT. In addition, many patients deviated from the inclusion criteria (RET mutation status, pretreatment, dose) (see Table 13 in Appendix B of the full dossier assessment). The 2 remaining studies (EXAM [12] and Wells 2012 [13]) are RCTs, each containing a placebo arm, with BSC (i.e. the ACT) being adequately implemented in both study arms. In the following, only the 2 studies on BSC are described (see Section 2.3.2.2).

2.3.2.1 Evidence on selpercatinib

Study LIBRETTO-001

The study 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. Both phases are described below. Table 11 and Table 12 in Appendix A of the full dossier assessment describe the study LIBRETTO-001.

Phase 1 of the LIBRETTO-001 study

Phase 1 of the LIBRETTO-001 study included patients aged 12 years and older with locally advanced or metastatic solid tumours, regardless of RET status and pretreatment, who had progressed on or were intolerant to previous standard therapies, for whom no standard therapy was available, for whom standard therapy was not indicated from the investigator's point of

view, or who refused standard therapy. The presence of an alteration of the RET gene was only an inclusion criterion after the minimum plasma concentration of selpercatinib specified in the study protocol had been reached. Treatment with certain drugs, e.g. cabozantinib and/or vandetanib was allowed, but presented no inclusion criterion.

MTD was determined according to a 3 + 3 algorithm based on the occurrence of dose-limiting toxicities (DLTs), with treatment to be discontinued if a DLT occurred. DLTs were pre-defined in the study protocol and included specific adverse events (AEs), e.g. febrile neutropenia of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3, occurring in cycle 1, i.e. within 28 days of the administration of the first dose. The dose steps to be administered (see Table 12 of the full dossier assessment) and the duration of the cycles per dose level (28 days) were also defined in the study protocol.

3 to 6 patients per dose level were treated to determine the MTD. MTD was achieved when at least 2 of the 3 to 6 patients had at least 1 DLT each. For each dose level, up to 15 additional patients could be included for further investigation of safety, pharmacokinetics and biological activity.

Following cycle 1, treatment was continued until occurrence of a discontinuation criterion (e.g. death, withdrawal of consent). The dose could be increased within the dose levels considered to be safe until the MTD was reached. In the event of progression, treatment was to be discontinued; however, it could be continued in consultation with the company if it was tolerated and the clinical benefit was assumed.

The MTD identified in phase 1 is 160 mg selpercatinib, orally, twice daily, in 28-day cycles. The dose corresponds to the dose for patients with a body weight of ≥ 50 kg recommended by the SPC. However, according to the SPC, patients with a body weight of < 50 should be administered 120 mg selpercatinib, orally, twice daily, in 28-day cycles [14].

In phase 1, 92 patients across all tumours were treated with a starting dose that did not correspond to the MTD. The proportion of patients who received a starting dose of 160 mg twice daily in phase 1 cannot be inferred from the information provided in Module 4 B. According to the study protocol, patients who received a starting dose of 160 mg twice daily and met the inclusion criteria for phase 2 could be considered for the analyses of the respective cohort of phase 2. It is also unclear to how many patients this applies.

Phase 2 of the LIBRETTO-001 study

In phase 2 of the LIBRETTO-001 study, patients aged 12 years and older with locally advanced or metastatic solid tumours with RET alteration were enrolled into the different cohorts presented in Table 11 of the full dossier assessment. Cohort 3, which is significantly relevant for the present therapeutic indication, included patients with advanced RET-mutant MTC and progression on or intolerance to standard therapy.

For all patients of phase 2, treatment started with 160 mg twice daily in 28-day cycles, irrespective of body weight; this does not correspond to the specifications of the SPC for patients with a body weight of < 50 kg. Treatment was continued until occurrence of unacceptable toxicity, or occurrence of another event that led to treatment discontinuation (e.g. death, withdrawal of consent). If AEs occurred, the dose could be reduced twice in steps of 80 mg per day. In the event of progression, treatment was to be discontinued; however, it could be continued in consultation with the company if it was tolerated and the clinical benefit was assumed.

Primary outcome in phase 2 was the objective response rate. Patient-relevant secondary outcomes were "overall survival", "morbidity", "health-related quality of life" and "side effects".

Recruitment for the LIBRETTO-001 study is still ongoing; 989 patients are to be recruited according to the registry entry as of 20 April 2021 [5].

Data cut-offs, analysis populations and presented results

According to the company, there are three data cut-offs for the LIBRETTO-001 study:

- First data cut-off: 17 June 2019 with 531 patients (interim analysis, based on the data provided by the company in the clinical study report [CSR])
- Second data cut-off: 16 December 2019 with 702 patients (interim analysis, which provides the basis for the European approval [15])
- Third data cut-off: 30 March 2020 with 746 patients (data cut-off requested by the Japanese regulatory authority; confirmatory data cut-off for the European approval [15]

Adults and adolescents 12 years and older with advanced RET-mutant MTC who require systemic therapy following treatment with cabozantinib and/or vandetanib are relevant for the present therapeutic indication. In Module 4 B, the company presented the results of the subpopulation of the LIBRETTO-001 study who met these criteria. The data presented by the company include patients from both phase 1 and phase 2; however, the company did not state how many patients from phase 1 were included and to which cohorts the included patients from phase 2 had been assigned. Since cohort 3 only comprised 118 patients at the second data cut-off and only 3 patients were added to the relevant subpopulation between data cut-off 2 and data cut-off 3, the patients in the subpopulation used by the company (see following description of the subpopulation) did not come exclusively from cohort 3.

For the therapeutic indication to be assessed, the company presented the results of the second data cut-off (150 patients) in Module 4 B and the results of the third data cut-off (153 patients) in the Appendix to Module 4 B of the full dossier assessment. The following considerations apply to the third data cut-off, because this includes more information than the second one.

In Module 4 B of the dossier, the company distinguished between 2 analysis populations, the safety analysis set (153 patients) and the efficacy analysis set (143 patients). While the safety analysis set included all patients who had received at least 1 dose of selpercatinib, the efficacy analysis set only included patients who had either been treated for ≥ 6 months or whose treatment had been discontinued within 6 months of initiation. This definition is not found in the study protocol or in the statistical analysis plan; although there is a similar analysis population, which, however, is only used as the basis for the additional analyses on tumour response. The company considered the patients of the efficacy analysis set for the analyses of the benefit outcomes. This procedure had no consequence in the present data situation, as no suitable data were available for the assessment of the added benefit.

In Module 4 B, the company presented results from the LIBRETTO-001 study. From the company's point of view, the intraindividual changes in the course of treatment with selpercatinib compared to the start of treatment show a reduction in symptom burden and an improvement in quality of life (with very low response rates to the questionnaires). Moreover, the company pointed out that the majority of patients achieved a better overall response under treatment with selpercatinib than under the treatment provided immediately before study inclusion.

2.3.2.2 Evidence on the ACT (BSC)

The company presented 2 studies (EXAM [12,16] and Wells 2012 [13]); these studies are RCTs, each containing a placebo arm, with BSC (the ACT) being adequately implemented in both study arms. These two studies have already been the subject of benefit assessments (see [17-20]), and the company cited the respective Modules 4 as sources in addition to the publications.

EXAM

The EXAM study is a double-blind, international, multicentre RCT on the comparison of cabozantinib with placebo. The study included 330 adult patients with unresectable locally advanced or metastatic MTC who had radiographically diagnosed progression within the last 14 month before study inclusion and who were randomly assigned in a 2:1 ratio to an intervention group in which cabozantinib was administered, or a control group in which placebo was administered. Stratification factors were age at the time of study inclusion (≤ 65 years vs. > 65 years) and pretreatment with tyrosine kinase inhibitor (TKI) (yes vs. no). The ITT population consisted of 219 patients in the intervention group and 111 patients in the control group. Presence of a RET alteration was no inclusion criterion. Therefore, not all patients had RET mutation of the tumour. In the control group, 62 (56%) patients had RET mutation of the tumour, of whom 45 (41% of the ITT population) had M918T RET mutations. Of the 111 patients in the control group, 64 (58%) had no prior systemic therapy and 47 (42%) had ≥ 1 prior systemic therapy. 9 (8%) patients were pretreated with vandetanib. Pretreatment with cabozantinib was an exclusion criterion. Primary outcome was PFS; the secondary outcomes

comprised overall survival, objective response rate, morbidity, health-related quality of life and side effects.

Analyses used by the company

In Module 4 B, the company describes that it used Kaplan-Meier curves, which are necessary for a comparison based on individual data, from the available sources of the EXAM study for overall survival and PFS (data cut-off of 28 August 2014). The Kaplan-Meier curves were digitised by the company to extract the underlying patient-specific data and were used for event time analyses. For overall survival in the placebo arm of the EXAM study, results are only available for patients with M918T RET mutation of the tumour (n = 45; with and without pretreatment with vandetanib) and for patients with and without RET mutation of the tumour (n = 111; with and without pretreatment with vandetanib). The sources used by the company provided no Kaplan-Meier curves for patients with RET mutation of the tumour and with and without pretreatment with vandetanib (n = 62). Kaplan-Meier curves are not available for the relevant subpopulation (RET mutation of the tumour and pretreatment with vandetanib), neither for overall survival nor for PFS.

Wells 2012

Wells 2012 is a double-blind, international, multicentre RCT on the comparison of vandetanib with placebo. The study included 331 adult patients with unresectable locally advanced or metastatic MTC who were randomly assigned in a 2:1 ratio to an intervention group in which vandetanib was administered, or a control group in which placebo was administered. Stratification was not carried out. The ITT population consisted of 231 patients in the intervention group and 100 patients in the control group. Presence of a RET alteration was no inclusion criterion. Therefore, not all patients had RET mutation of the tumour. In the control group, 50 (50%) patients had RET mutation of the tumour, of whom ≥ 41 (≥ 41% of the ITT population) had M918T RET mutations. Of the 100 patients in the control group, 58 (58%) had no prior systemic therapy and 42 (42%) had ≥ 1 prior systemic therapy. Information on pretreatment with cabozantinib is not available. The proportion is probably very minor, since cabozantinib was approved after vandetanib. Primary outcome was PFS; the secondary outcomes comprised overall survival, morbidity, health-related quality of life and side effects.

Analyses used by the company

In Module 4 B, the company describes that no Kaplan Meier curves were available for the various outcomes for the 50 patients in the placebo arm with RET mutation of the tumour. Accordingly, the company only performed descriptive comparisons for the Wells 2012 study, in which it compares the median values of PFS and the objective response rate.

2.3.3 Assessment of the evidence presented by the company

The data presented by the company in Module 4 B are unsuitable for the assessment of the added benefit of selpercatinib versus the ACT (BSC). This is explained below.

The non-controlled study LIBRETTO-001 permits no conclusions on the added benefit

The company presented the results of the non-controlled LIBRETTO-001 study and performed descriptive considerations of the results. When describing the added benefit, the company also referred to intraindividual comparisons on best response according to imaging techniques under the last treatment before study inclusion and under treatment with selpercatinib.

The results from the LIBRETTO-001 study alone are not suitable for the assessment of the added benefit of selpercatinib compared to the ACT (BSC), as they do not allow a comparison with the ACT.

Deviations from the specifications of the SPC

In the results presented by the company, there are also deviations from the specifications of the SPC for the subpopulation of the LIBRETTO-001 study operationalized by the company (153 patients of the third data cut-off):

- The starting dose deviated from the dose recommended in the SPC in 40 (26%) patients.
- Information on the proportion of patients who received an approval-compliant maintenance dose (160 mg twice daily or 120 mg twice daily). From the available information, it can be estimated that between 9 (5.9%) and 32 (20.9%) patients did not receive the correct maintenance dose.
- 31 (20.3%) patients were treated beyond progression, contrary to the specifications of the SPC.

The interpretability of the results from the LIBRETTO-001 study presented by the company is limited, since the proportion of patients with deviations from the specifications of the SPC is at least 26% even assuming the greatest possible overlap.

Comparison of individual arms from different studies not suitable for conclusions on the added benefit

For the comparison of selpercatinib with the ACT (BSC), the company compared the population of the LIBRETTO-001 study (n = 124 [second data cut-off] and n = 143 [third data cut-off]) pretreated with cabozantinib and/or vandetanib with the EXAM study for the outcomes “overall survival” and “PFS” and compared the populations listed in Table 6.

The company conducted the comparisons of individual arms from different studies in unweighted manner and additionally using the propensity score method (weighted according to age, gender, ECOG status, smoking status, present RET mutation). The company performed the comparison only for the EXAM study, as a comparison for the Wells 2012 study was not possible due to a lack of data on the suitable subpopulation.

For the outcomes of side effects, the company presented descriptive comparisons on the number of patients with at least one event. In doing so, it compared the results for the overall rates (AEs,

severe AEs [CTCAE grade ≥ 3], SAEs, discontinuation due to AEs) as well as for diarrhoea and hypertension from the LIBRETTO-001 study with the control arms of EXAM and Wells 2012, taking into account all patients in the control arms regardless of RET mutation status.

In an overall consideration of the available evidence (LIBRETTO-001 and comparison of individual arms), the company derived a hint of a non-quantifiable added benefit for selpercatinib from the results presented.

The comparison of individual arms from different studies is not suitable for conclusions on the added benefit because:

- the patients on the comparator side (EXAM study) did not meet the inclusion criteria of the research question, in particular, there was no restriction to patients pretreated with vandetanib and/or cabozantinib and largely no comparable operationalization of the RET mutation status
- other than postulated by the company, direction and magnitude of potential biases due to known (in particular pretreatment and RET mutation status) as well as unknown confounders cannot be assessed and furthermore
- there are doubts that the patients in the studies LIBRETTO and EXAM are comparable in their prognosis.

In the present data situation, the effects in overall survival observed in the comparison are altogether not large enough that they could not be explained by bias alone.

This is explained in detail below.

Deviations from the inclusion criteria in the studies on the ACT presented by the company

In the 2 RCTs (EXAM [12] and Wells 2012 [13]), which each contain data on BSC in the placebo arm, there are major deviations from the inclusion criteria with regard to RET mutation status and prior systemic therapy with cabozantinib or vandetanib (see Table 5); for instance, the majority of patients in the studies on the comparator side were not pretreated. Analyses for the subpopulations of pretreated patients with RET mutation corresponding to the present research question are missing in the sources used by the company.

Table 5: Deviation from inclusion criteria in the placebo arm of the RCTs EXAM and Wells 2012

Study	Design	Population	Deviation from inclusion criteria in the placebo arm
EXAM [12,16]	RCT, cabozantinib 140 mg/day vs. placebo[a]	219 vs. 111 patients ≥ 18 years with unresectable, locally advanced or metastatic MTC who had radiographically diagnosed progression within the last 14 months before study inclusion with and without pretreatment	▪ RET mutation status [b] ▫ positive: n = 62 (56%), of whom n = 45 (41%) had M918T mutation ▫ negative: n = 11 (10%) ▫ unknown: n = 38 (34%) ▪ systemic pretreatment with vandetanib: ▫ total population: n = 9 (8%) ▫ total population with RET mutation: n ≤ 9 (≤ 13%)[c]
Wells 2012 (ZETA) [13,21]	RCT, vandetanib 300 mg/day vs. placebo[a]	231 vs. 100 patients ≥ 18 years with measurable, unresectable, locally advanced or metastatic MTC with and without pretreatment	▪ RET mutation status[d] ▫ positive: n = 50 (50%), of whom n = ≥ 41 (≥ 41%) had M918T mutation[c] ▫ negative: n = 33 (33%) ▫ unknown: n = 17 (17%) ▪ systemic pretreatment: n = 42 (42%). probably only a few with cabozantinib, since cabozantinib was approved after vandetanib

a. BSC was adequately implemented in both study arms.
b. Data from the supplement Table S1 on [16].
c. More detailed information was not possible on the basis of the available results.
d. Information on post-hoc analyses in [21].

BSC: best supportive care; MTC: medullary thyroid cancer; n: number of patients in the category; RCT: randomized controlled trial; RET: rearranged during transfection

Sensitivity analyses on the comparison of individual arms (LIBRETTO-001 vs. EXAM) not meaningful

As no analyses were available for the EXAM study for the subpopulations of patients with RET mutation pretreated with cabozantinib and/or vandetanib corresponding to the present research question, the company presented 3 sensitivity analyses in addition to a main analysis for its comparisons of individual arms (see Table 6).

In the main analysis, the company used patients with M918T mutation on the placebo side, the majority of whom (approx. 90%) were not pretreated and therefore did not correspond to the present research question. The comparison of the main analysis is therefore not interpretable due to the large differences between the populations. With sensitivity analysis 1, the company wanted to show that the possible bias resulting from the differences in pretreatment (pretreated population in the LIBRETTO-001 study vs. the largely treatment-naive population in the EXAM study) was to the disadvantage of selpercatinib.

Table 6: Results on overall survival, LIBRETTO-001 study vs. EXAM study

Analysis	**Selpercatinib**	**BSC (EXAM)**	**Median (months) effect, HR [95% CI]; p-value (unweighted)[a]**
Main analysis	RET mutation, pretreated[b] N = 143	M918T mutation, approx. 90% treatment-naive[c] N = 45	33.2 [33.2; NC] vs. 18.7 [14; 35.3] **0.36 [0.21; 0.62]**; p < 0.001
Sensitivity analysis 1	RET mutation, Pretreated[b] and treatment-naive N = 255	M918T mutation, approx. 90% treatment-naive[c] N = 45	33.2 [33.2; NC] vs. 18.7 [14; 35.3] **0.23 [0.13; 0.39]**, p < 0.001
Sensitivity analysis 2	RET mutation, pretreated[b] N = 143	With and without RET mutation, 92% treatment-naive[c, d] 78% without pretreatment with TKI N = 111	33.2 [33.2; NC] vs. 21.2 [17.2; 34.2] **0.40 [0.25; 0.64]**; p < 0.001
Sensitivity analysis 3	M918T mutation, pretreated[b] N = 98	M918T mutation, approx. 90% treatment-naive[c] N = 45	33.2 [33.2; NC] vs. 18.7 [14; 35.3] **0.48 [0.27; 0.86]**, p = 0.013

a. Using the propensity score method, the results are largely comparable.
b. Cabozantinib and/or vandetanib.
c. Vandetanib.
d. Institute's calculation.

BSC: best supportive care; N: number of patients; NC: not calculable; RET: rearranged during transfection; TKI: tyrosine kinase inhibitor

However, sensitivity analysis 1 is not meaningful primarily because the majority of treatment-naive patients were still included also in this analysis on the comparison side (EXAM). The subgroup analyses of the total population from the EXAM study [22] also show that in the placebo arm of the EXAM study, 14 (58.3%) of the 24 patients who had received pretreatment with TKIs died after a median period of 24.7 months, while 44 (51.2%) of the 86 patients who had not been treated with TKIs died earlier, namely after a median period of 20.3 months. This speaks against the company's postulate stating that pretreatment leads to shorter overall survival. Moreover, in sensitivity analysis 1, the group with the worst overall survival (the group with M918T mutation) is considered with regard to the mutation on the comparator side (EXAM), and thus sensitivity analysis 1 is also biased by the factors RET mutation and pretreatment.

With the help of sensitivity analyses 2 and 3, the company tried to show the impact of the differences in overall survival in the presence or absence of an RET alteration or an RET M918T mutation found in the Exam study. However, it was notable that the comparison in sensitivity analysis 3, which compared patients with RET M918T mutation (i.e. similar populations in terms of mutation), was not as favourable for selpercatinib as in the main analysis, which compared patients with RET mutation versus patients with RET M918T

mutation. Finally, it remains unclear, also on the basis of the sensitivity analyses presented, what bias arised from the fact that no analyses for the subpopulations corresponding to the present research question were available from the EXAM study.

Another potentially biasing factor is the presence of a progression at study inclusion. This was an inclusion criterion in the EXAM study (radiologically documented progression within the last 14 months) but not in the Wells 2012 study. This difference between the study populations of EXAM and Wells 2012 is, for instance, emphasised in the publication on the LIBRETTO-001 study (Wirth 2020 [3]), in the ESMO guideline [23] and in a recent review on the impact of the RET alteration (Salvatore 2021 [24]). In this context, the publications also address the fact that the median PFS in the EXAM study (11 vs. 4 months) was significantly shorter than in the Wells 2012 study (30 vs. 19 months). It is not clear from the available results whether the study population of the LIBRETTO-001 study is more similar to the study population of the Wells 2012 study or the study population of the EXAM study. Thus, it is unclear whether the benefit of selpercatinib compared to BSC described by the company is due to selpercatinib or to the differences in the study population.

In summary, the comparison of selpercatinib (LIBRETTO-001) with BSC (placebo arm of the RCT EXAM) aimed for by the company is potentially biased by systemic pretreatment, RET mutation status, progression at study inclusion and potential other unknown confounding factors.

No usable results on side effects

In its consideration on side effects, the company compared the proportion of patients with event. These comparisons cannot be interpreted in the present situation, as the treatment and observation duration varied greatly between the studies. Thus, the present results for the outcomes on side effects would not be interpretable even if the similarity of the studies were given.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of selpercatinib in comparison with the ACT (BSC). The results from the non-controlled study LIBRETTO-001 alone are not suitable for the benefit assessment, as data on the ACT are not available. Moreover, the comparisons of individual arms from different studies presented by the company are not suitable for conclusions on the added benefit, as not all inclusion criteria of the research question are fulfilled in the two studies on the comparator therapy submitted by the company and the resulting bias with regard to size and direction cannot be assessed on the basis of the sensitivity analyses submitted by the company. Moreover, the effects are not large enough that they could not be explained by bias alone. Finally, a weighing of benefits and harms would not be possible because the results on side effects are not interpretable.

2.4 Results on added benefit

Suitable data for the assessment of the added benefit of selpercatinib in comparison with the ACT (BSC) 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 are not available. This resulted in no hint of an added benefit of selpercatinib in comparison with the ACT (BSC); an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of selpercatinib in comparison with the ACT is summarized in Table 7.

Table 7: 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 MTC cancer who require systemic therapy following treatment with cabozantinib and/or vandetanib	BSC[b]	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. The determination of the ACT was based on the assumption that curative treatment measures were no longer indicated. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer; RET: rearranged during transfection		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of the second data cut-off of the non-controlled LIBRETTO-001 study and 6 other studies.

The G-BA decides on the added benefit.

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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