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Selpercatinib (RET fusion-positive 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-Fusions-positives 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)
MTC	medullary thyroid cancer
MTD	maximum tolerable dose
RCT	randomized controlled trial
RET	rearranged during transfection
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 with advanced rearranged during transfection (RET) fusion-positive thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib.

The research questions shown in Table 2 resulted from the ACT specified by the G-BA and the subdivision of the patient population according to the degree of differentiation.

Table 2: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced RET fusion-positive differentiated (papillary or follicular) thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]
2	Adults with advanced RET fusion-positive anaplastic thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]

a. Presentation of the respective 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. BSC 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; RET: rearranged during transfection

The G-BA distinguished between differentiated (papillary or follicular) thyroid cancer and anaplastic thyroid cancer and specified the same ACT for both subpopulations.

The company followed the G-BA's specification on the ACT. However, it did not differentiate between the two questions, but considered them together. Since usable data were not available for either of the two subpopulations named by the G-BA, both research questions are assessed below in joint sections of the report.

The assessment was 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 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 for both research questions.

Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it additionally conducted an information retrieval for further studies for a comparison of individual arms from Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it additionally conducted an information retrieval for further studies for a comparison of individual arms from different studies involving the ACT. Since the company found not studies on the ACT, it only presented the non-controlled approval study LIBRETTO-001.

Evidence provided by the company

The basket study LIBRETTO-001 on selpercatinib 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. sorafenib and/or lenvatinib was allowed, but presented no inclusion criterion.

Aim of phase 1 was the determination of the medullary thyroid cancer (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, a subpopulation of the cohort with advanced or metastatic solid tumours with RET fusion and progression on or intolerance to standard treatment 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".

Presented results on outcome level

Patients with advanced RET fusion-positive thyroid cancer who require systemic therapy treatment with sorafenib and/or lenvatinib are relevant for both research questions of the present therapeutic indication. The company presented results of a subpopulation of the LIBRETTO-001 study. This subpopulation consisted of 21 patients, of whom 19 patients met all of these criteria; however, 2 patients had not been pretreated with sorafenib and/or lenvatinib.

18 (86%) of the 21 patients of the third data cut-off had differentiated thyroid cancer (17 with papillary carcinoma and 1 with Hürthle cell carcinoma), another 2 (10%) patients had poorly differentiated thyroid cancer, and 1 (5%) patient had anaplastic thyroid cancer.

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.

Assessment of the evidence presented by the company

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

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. In the dossier, the company also presented no other supporting data that would allow a classification of the results from the non-controlled study.

Deviations from the specifications of the SPC

The interpretability of the results presented by the company is limited, as the specifications of the SPC are not met for at least 7 (33%) of the 21 patients in the subpopulation operationalized by the company. This concerns deviations from the dosage, treatment beyond progression and pretreatment with sorafenib and / or lenvatinib. These deviations had no consequence, since data permitting a comparison with the ACT are not available.

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 in the present therapeutic indication.

Table 3: Selpercatinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced RET fusion-positive differentiated (papillary or follicular) thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]	Added benefit not proven
2	Adults with advanced RET fusion-positive anaplastic thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]	Added benefit not proven

a. Presentation of the respective 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; 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 with advanced RET fusion-positive thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA and the subdivision of the patient population according to the degree of differentiation.

[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 questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[a]
1	Adults with advanced RET fusion-positive differentiated (papillary or follicular) thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]
2	Adults with advanced RET fusion-positive anaplastic thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]

a. Presentation of the respective 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. BSC 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; RET: rearranged during transfection

The G-BA distinguished between differentiated (papillary or follicular) thyroid cancer and anaplastic thyroid cancer and specified the same ACT for both subpopulations.

The company followed the G-BA's specification on the ACT. However, it did not differentiate between the two questions, but considered them together. Since usable data are not available for either of the two subpopulations named by the G-BA, both research questions are assessed below in joint sections of the report (see Section 2.3, 2.4and Section 2.5).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

For both research questions, 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 23 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 23 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 B 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 for a comparison of individual arms from different studies. Since the company found not studies on the ACT, it only presented the non-controlled approval study LIBRETTO-001.

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 submitted the basket study LIBRETTO-001 [3-7]. LIBRETTO-001 is an ongoing, non-controlled, prospective 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 9 and Table 10 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. sorafenib and/or lenvatinib 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 10 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 kg were to be administered 120 mg selpercatinib, orally, twice daily, in 28-day cycles [8].

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 C. 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 9 of the full dossier assessment. Cohort 1, which is relevant for the present indication, included patients with advanced or metastatic solid tumours with RET fusion 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 and 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 [9])
- 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 [9])

Patients with advanced RET fusion-positive thyroid cancer who require systemic therapy treatment with sorafenib and/or lenvatinib are relevant for both research questions of the present therapeutic indication. In Module 4 C, the company presented results of a subpopulation of the LIBRETTO-001 study. 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 had been considered. The data on treatment and study disposition show that these were at least 7 (33%) patients.

For the therapeutic indication to be assessed, the company presented the results of the second data cut-off (19 patients) in Module 4 C and the results of the third data cut-off (21 patients) in the Appendix to Module 4 C of the full dossier assessment. The following considerations apply to the third data cut-off, because this includes more information than the second one.

18 (86%) of the 21 patients of the third data cut-off had differentiated thyroid cancer (17 with papillary carcinoma and 1 with Hürthle cell carcinoma), another 2 (10%) patients had poorly differentiated thyroid cancer, and 1 (5%) patient had anaplastic thyroid cancer.

In the dossier, the company distinguished between 2 analysis populations, the safety analysis set (21 patients) and the efficacy analysis set (18 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 C, 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, although the low response rates to the questionnaires permit no reliable conclusion. 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. From the results presented, the company derived a hint of a non-quantifiable added benefit for selpercatinib.

2.3.3 Assessment of the evidence presented by the company

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

The company only 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. In the dossier, the company also presented no other supporting data that would allow a classification of the results from the non-controlled study.

Deviations from the specifications of the SPC

Irrespective of the fact that no comparative data are available, the interpretability of the presented results of the LIBRETTO-001 study is limited, as the specifications of the SPC are not fulfilled for all 21 patients of the third data cut-off in the subpopulation operationalized by the company:

- The starting dose deviated from the starting dose recommended in the SPC in 7 (33.3%) patients; of whom all 7 patients were presumably included during phase 1.
- The maintenance dose for the 2 (9.5%) patients with a body weight of < 50 kg was 160 mg twice daily instead of 120 mg twice daily.
- 6 (28.6%) patients were treated beyond progression, contrary to the specifications of the SPC.
- 2 (9.5%) patients had not been pretreated with sorafenib and/or lenvatinib.

This means that the proportion of patients with deviations from the requirements of the SPC is at least 33%, even assuming the greatest possible overlap. These deviations had no consequence in the present situation, since data permitting a comparison with the ACT are not available.

2.4 Results on added benefit

Suitable data for the assessment of the added benefit of selpercatinib in comparison with the ACT (BSC) in adult patients with advanced RET fusion-positive thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib 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 5.

Table 5: Selpercatinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with advanced RET fusion-positive differentiated (papillary or follicular) thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]	Added benefit not proven
2	Adults with advanced RET fusion-positive anaplastic thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib	BSC[b]	Added benefit not proven

a. Presentation of the respective 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; RET: rearranged during transfection

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

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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