Selpercatinib
(RET fusion-positive thyroid cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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

The questionnaire on the disease and its treatment was answered by Harald Rimmele.

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 15 May 2024.

Research question

The aim of the present report is the assessment of the added benefit of selpercatinib in comparison with the appropriate comparator therapy (ACT) for first-line treatment in adults and adolescents 12 years and older with advanced rearranged during transfection (RET) fusion-positive, radioiodine-refractory thyroid cancer (when radioiodine is appropriate) as well as in adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[a, b]
1	Adults and adolescents 12 years and older with advanced RET fusion-positive, radioiodine-refractory thyroid cancer, first-line treatment[c]	▪ Sorafenib or ▪ lenvatinib (for adults only)
2	Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor	Individualized treatment selected from ▪ sorafenib, ▪ lenvatinib[d], and ▪ best supportive care[e] taking into account previous therapy and general health

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that curative treatment measures and local treatment options are no longer being considered.
c. The G-BA assumes that, based on their symptoms, patients have an indication for systemic antineoplastic therapy and that, therefore, a watch-and-wait strategy, among other things, is not an option.
d. Lenvatinib is not approved for adolescents in the present therapeutic indication. In accordance with the generally recognized state of medical knowledge, the G-BA states that off-label use of lenvatinib as part of individualized treatment, taking into account previous therapy and general health, is considered a standard of care for adolescents and is generally to be preferred over the drugs approved to date for the therapeutic indication.
e. Best supportive care refers to the therapy which 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; RET: rearranged during transfection

The company deviated from the G-BA's specification on the ACT. It subdivided the patient population for research question 1 into further subpopulations (adolescents 12 years and older, adults with differentiated thyroid cancer and adults with anaplastic thyroid cancer) and names separate ACTs for each. Here, the company referred to the consultation meeting with the G-BA of 13 July 2022 and the G-BA decision on the previous benefit assessment procedure on selpercatinib in adults with advanced RET fusion-positive thyroid cancer who require systemic therapy after treatment with sorafenib and/or lenvatinib. The company stated that it expanded the patient populations specified by the G-BA in the consultation to include the subpopulation of adolescents aged 12 years and older, including the ACT, because the therapeutic indication was extended to include adolescents aged 12 years and older after the consultation.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA.

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

Results

The check of the information retrieval did not identify any relevant randomized controlled trials (RCTs) for the direct comparison of selpercatinib versus the ACT for either of the two research questions.

As the company itself did not identify any RCTs for the direct comparison of selpercatinib versus the ACT, it conducted an information retrieval for further investigations on selpercatinib. In doing so, it identified the two single-arm studies LIBRETTO-001 and LIBRETTO-121, on the basis of which selpercatinib was approved in the present therapeutic indication, and used these as the best available evidence for assessing the added benefit. The company conducted no information retrieval on further investigations with the ACT.

The two studies included by the company are uncontrolled, ongoing, prospective basket studies for the treatment of adults (LIBRETTO-001) and children and adolescents aged up to 21 years (LIBRETTO-121) with selpercatinib. These are not suitable for the benefit assessment, as they do not allow a comparison of selpercatinib with the ACT due to the lack of a comparator arm in each case. This applies to both research questions.

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. This applies to both research questions.

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.

[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 3: Selpercatinib – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a, b]**	**Probability and extent of added benefit**
1	Adults and adolescents 12 years and older with advanced RET fusion-positive, radioiodine-refractory thyroid cancer, first-line treatmentc	▪ Sorafenib or ▪ lenvatinib (for adults only)	Added benefit not proven
2	Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor	Individualized treatment selected from ▪ sorafenib, ▪ lenvatinib[d], and ▪ best supportive care[e] taking into account previous therapy and general health	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that curative treatment measures and local treatment options are no longer being considered.
c. The G-BA assumes that, based on their symptoms, patients have an indication for systemic antineoplastic therapy and that, therefore, a watch-and-wait strategy, among other things, is not an option.
d. Lenvatinib is not approved for adolescents in the present therapeutic indication. In accordance with the generally recognized state of medical knowledge, the G-BA states that off-label use of lenvatinib as part of individualized treatment, taking into account previous therapy and general health, is considered a standard of care for adolescents and is generally to be preferred over the drugs approved to date for the therapeutic indication.
e. Best supportive care refers to the therapy which 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; RET: rearranged during transfection

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of selpercatinib in comparison with the ACT for first-line treatment in adults and adolescents 12 years and older with advanced RET fusion-positive, radioiodine-refractory thyroid cancer (when radioiodine is appropriate) as well as in adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of selpercatinib

Research question	Therapeutic indication	ACT[a, b]
1	Adults and adolescents 12 years and older with advanced RET fusion-positive, radioiodine-refractory thyroid cancer, first-line treatment[c]	▪ Sorafenib or ▪ lenvatinib (for adults only)
2	Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor	Individualized treatment selected from ▪ sorafenib, ▪ lenvatinib[d], and ▪ best supportive care[e] taking into account previous therapy and general health

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that curative treatment measures and local treatment options are no longer being considered.
c. The G-BA assumes that, based on their symptoms, patients have an indication for systemic antineoplastic therapy and that, therefore, a watch-and-wait strategy, among other things, is not an option.
d. Lenvatinib is not approved for adolescents in the present therapeutic indication. In accordance with the generally recognized state of medical knowledge, the G-BA states that off-label use of lenvatinib as part of individualized treatment, taking into account previous therapy and general health, is considered a standard of care for adolescents and is generally to be preferred over the drugs approved to date for the therapeutic indication.
e. Best supportive care refers to the therapy which 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; RET: rearranged during transfection

The company deviated from the G-BA's specification on the ACT. It subdivided the patient population for research question 1 into further subpopulations (adolescents 12 years and older, adults with differentiated thyroid cancer, and adults with anaplastic thyroid cancer) and names separate ACTs for each. Here, the company referred to the consultation meeting with the G-BA of 13 July 2022 and the G-BA decision on the previous benefit assessment procedure on selpercatinib in adults with advanced RET fusion-positive thyroid cancer who require systemic therapy after treatment with sorafenib and/or lenvatinib [3]. The company stated that it expanded the patient populations specified by the G-BA in the consultation to include

the subpopulation of adolescents aged 12 years and older, including the ACT, because the therapeutic indication was extended to include adolescents aged 12 years and older after the consultation.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the ACT specified by the G-BA will not be further commented on below because the company did not present any suitable data for the benefit assessment – neither compared to a comparator therapy designated by the company nor compared to the ACT specified by the G-BA (see Chapter I 3). Since no suitable data are therefore available for either of the 2 research questions, the assessment of both research questions is presented in the following in joint report sections.

The assessment was conducted versus the ACT specified by the G-BA 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: 4 April 2024)
- bibliographical literature search on selpercatinib (last search on 4 April 2024)
- search in trial registries/trial results databases for studies on selpercatinib (last search on 4 April 2024)
- search on the G-BA website for selpercatinib (last search on 4 April 2024)

To check the completeness of the study pool:

- search in trial registries for studies on selpercatinib (last search on 31 May 2024); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

Concurring with the company's assessment, the check did not identify any relevant randomized controlled trials (RCTs) for the direct comparison of selpercatinib versus the ACT specified by the G-BA.

Further investigations

As the company itself did not identify any RCTs for the direct comparison of selpercatinib versus the ACT, it conducted an information retrieval for further investigations on selpercatinib. In doing so, it identified the two single-arm studies LIBRETTO-001 [4] and LIBRETTO-121 [5], on the basis of which selpercatinib was approved in the present therapeutic indication, and used these as the best available evidence for assessing the added benefit. The company conducted no information retrieval on further investigations with the ACT.

A check for completeness of the study pool presented by the company for other investigations was waived because the data submitted by the company under "Other investigations" are unsuitable for the benefit assessment. The following describes the 2 studies of the company and justifies their unsuitability.

Evidence presented by the company

The company included the 2 uncontrolled, single-arm studies LIBRETTO-001 and LIBRETTO-121 in its assessment. However, the two studies are ongoing, prospective basket studies for the treatment of adults (LIBRETTO-001) and children and adolescents aged up to 21 years (LIBRETTO-121) with selpercatinib.

LIBRETTO-001 study

The LIBRETTO-001 study included adult patients with advanced or metastatic solid tumours who had progressed under or were intolerant to previous standard therapy or for whom no curative standard therapy existed, for whom standard therapy was not suitable according to the investigator's assessment or who refused standard therapy. In some study centres (not so in Germany, South Korea and Canada), the inclusion of patients 12 years and older was also possible once permission had been granted. The study consists of 2 phases. In the first phase, which has already been completed, dose escalation was carried out to determine the maximum tolerated dose of selpercatinib. In phase 2 of the study, which is still ongoing, the maximum tolerated dose of selpercatinib is being used in several cohorts of patients with an alteration in the RET gene, including RET fusions. Patients were enrolled in the different cohorts depending on their primary tumour, previous therapy, potential therapy, and RET status. In phase 2 of the study, all patients were treated with 160 mg selpercatinib twice daily until disease progression, unacceptable toxicity, or discontinuation for other reasons. Weight-dependent dosing according to the Summary of Product Characteristics (SPC) [6] was not provided. The primary outcome of the 2nd study phase was the objective response rate. The LIBRETTO-001 study enrolled patients on an ongoing basis and evaluated the results in several data cut-offs. A total of 968 patients were enrolled by the most recent 6th data cut-off on 13 January 2023.

In its benefit assessment, the company included data on the 4th data cut-off from 15 June 2021 for research question 1 (first-line therapy). To this end, it presents results from a subpopulation of 18 adult patients with advanced RET fusion-positive thyroid cancer who have received no previous therapy apart from radioiodine therapy. Patients aged < 18 years with RET fusion-positive thyroid cancer were not included in the LIBRETTO-001 study, regardless of previous therapy. Thus, the LIBRETTO-001 study does not include any patients from research question 2. In addition, the company presented analyses on the most recent 6th data cut-off from 13 January 2023 for adult patients with advanced RET fusion-positive thyroid cancer in first-line treatment (research question 1; N = 24), as well as for those who require further systemic therapy after previous therapy with sorafenib and/or lenvatinib. The latter are not the subject of this benefit assessment (see Chapter I 2).

LIBRETTO-121 study

The LIBRETTO-121 study included patients aged between 6 months and 21 years with locally advanced or metastatic solid tumours or primary tumours of the central nervous system who had relapsed or progressed on available therapies, who had not responded to available therapies and for whom no standard therapy or available curative systemic therapy existed. Like the LIBRETTO-001 study, the LIBRETTO-121 study also consists of 2 study phases, of which the 1st phase (dose escalation to determine the maximum tolerated dose) has been completed and the 2nd study phase (application of the determined maximum tolerated dose

of selpercatinib in patients with an alteration in the RET gene, including RET fusions, in several cohorts depending on the primary tumour) is still ongoing. Treatment for all phase 2 patients was given at a dose of 92 mg/m^2 body surface area (with a maximum dose of 160 mg) twice daily. This deviates from the SPC specifications [6], which provide for body weight-dependent dosing of selpercatinib. The primary outcome of the 2nd study phase of the LIBRETTO-121 study was the objective response rate, as in the LIBRETTO-001 study.

In its benefit assessment, the company summarized the results of the 8 patients aged < 18 years with advanced RET fusion-positive papillary thyroid cancer in first-line treatment included in the only data cut-off of the LIBRETTO-121 study to date (first interim analysis from 13 January 2023) for research question 1. The LIBRETTO-121 study did not include pretreated adolescents 12 years and older with advanced RET fusion-positive thyroid cancer. Therefore, the study does not provide any data for research question 2.

Assessment of the evidence presented by the company

The uncontrolled studies LIBRETTO-001 and LIBRETTO-121 presented by the company in Module 4 C are not suitable for the benefit assessment, as they do not allow a comparison of selpercatinib with the ACT due to the lack of a comparator arm in each case. This applies to both research questions.

I 4 Results on added benefit

For the assessment of selpercatinib for first-line treatment in adults and adolescents aged 12 years and older with advanced RET fusion-positive, radioiodine-refractory thyroid cancer (when radioiodine is appropriate [research question 1]) and for adolescents aged 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor (research question 2), no suitable data are available in each case compared to the ACT. There is no hint of an added benefit of selpercatinib in comparison with the ACT in each case; an added benefit is therefore not proven in either case.

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

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Adults and adolescents 12 years and older with advanced RET fusion-positive, radioiodine-refractory thyroid cancer, first-line treatment[c]	▪ Sorafenib or ▪ lenvatinib (for adults only)	Added benefit not proven
2	Adolescents 12 years and older with advanced RET fusion-positive thyroid cancer after previous therapy with a protein kinase inhibitor	Individualized treatment selected from ▪ sorafenib, ▪ lenvatinib[d], and ▪ best supportive care[e] taking into account previous therapy and general health	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that curative treatment measures and local treatment options are no longer being considered.
c. The G-BA assumes that, based on their symptoms, patients have an indication for systemic antineoplastic therapy and that, therefore, a watch-and-wait strategy, among other things, is not an option.
d. Lenvatinib is not approved for adolescents in the present therapeutic indication. In accordance with the generally recognized state of medical knowledge, the G-BA states that off-label use of lenvatinib as part of individualized treatment, taking into account previous therapy and general health, is considered a standard of care for adolescents and is generally to be preferred over the drugs approved to date for the therapeutic indication.
e. Best supportive care refers to the therapy which 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; RET: rearranged during transfection

For research question 1, the assessment described above deviates from that of the company. The company subdivides the patient population for research question 1 into further subpopulations (adolescents 12 years and older, adults with differentiated thyroid cancer, and adults with anaplastic thyroid cancer) and derives one hint each for a non-quantifiable, but at least minor added benefit. For research question 2, the assessment described above corresponds to that of the company.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-62.html.