Selpercatinib
(RET fusion-positive solid tumours)

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

No feedback was received in the framework of the present dossier assessment.

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Selpercatinib, Neoplasms, Gene Fusion, Benefit Assessment

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)
NSCLC	non-small cell lung cancer
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 best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with rearranged during transfection (RET) fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted.

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

Table 2: Research question of the benefit assessment of selpercatinib

Therapeutic indication	**ACT[a]**
Adults with advanced RET fusion-positive solid tumours[b], when treatment options not targeting RET provide limited clinical benefit, or have been exhausted	Best supportive care[c]
a. Presented is the ACT specified by the G-BA. b. NSCLC and thyroid cancer are not covered by the present therapeutic indication. Separate therapeutic indications for selpercatinib exist for these two indications. c. 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; NSCLC: non-small cell lung cancer; RET: rearranged during transfection	

On 28 May 2024, the G-BA passed a resolution specifying the ACT. In its dossier, however, the company referred to the consultation with the G-BA in September 2022 and, in deviation from the resolution, chose as the ACT an individualized treatment choosing from tumour-specific standard therapy and BSC, taking into account the histology and the respective disease and treatment stage.

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 present assessment is carried out in comparison with the G-BA's ACT.

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

Concurring with the company, no randomized controlled trial (RCT) on the direct comparison of selpercatinib versus the ACT was identified from the check of the completeness of the study pool.

As the company did not identify any RCT 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 single-arm study LIBRETTO-001. The company has conducted no information retrieval on other investigations for the ACT.

The study included by the company is an uncontrolled, ongoing, prospective basket study for the treatment of adults with selpercatinib. It is not suitable for the benefit assessment, as it does not allow a comparison of selpercatinib with the ACT due to the lack of a comparator arm.

Results on added benefit

No suitable data are available for the benefit assessment of selpercatinib in patients with advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted. There is no hint of an added benefit of selpercatinib in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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

Therapeutic indication	**ACTa**	**Probability and extent of added benefit**
Adults with advanced RET fusion-positive solid tumours[b], when treatment options not targeting RET provide limited clinical benefit, or have been exhausted	Best supportive care[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.

b. NSCLC and thyroid cancer are not covered by the present therapeutic indication. Separate therapeutic indications for selpercatinib exist for these two indications.

c. 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; NSCLC: non-small cell lung cancer; 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 best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with rearranged during transfection (RET) fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted.

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

Table 4: Research question of the benefit assessment of selpercatinib

Therapeutic indication	**ACTa**
Adults with advanced RET fusion-positive solid tumours[b], when treatment options not targeting RET provide limited clinical benefit, or have been exhausted	Best supportive care[c]
a. Presented is the ACT specified by the G-BA. b. NSCLC and thyroid cancer are not covered by the present therapeutic indication. Separate therapeutic indications for selpercatinib exist for these two indications. c. 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; NSCLC: non-small cell lung cancer; RET: rearranged during transfection	

On 28 May 2024, the G-BA passed a resolution specifying the ACT. In its dossier, however, the company referred to the consultation with the G-BA in September 2022 and, in deviation from the resolution, chose as the ACT an individualized treatment choosing from tumour-specific standard therapy and BSC, taking into account the histology and the respective disease and treatment stage.

The present assessment is carried out in comparison with the G-BA's ACT. 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.

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, no RCT on the direct comparison of selpercatinib versus the ACT was identified from the check of the completeness.

Further investigations

As the company did not identify any RCT 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 single-arm study LIBRETTO-001 [3]. The company has conducted no information retrieval on other investigations for the ACT.

Since the company did not conduct a comparison with the ACT, the data presented are not suitable for deriving conclusions on the added benefit of selpercatinib in the present therapeutic indication. Therefore, the completeness of the study pool for further investigations was not checked.

Evidence provided by the company

The company included the single-arm study LIBRETTO-001 in its benefit assessment. As justification, the company stated that the study represents the best available evidence for the assessment of the medical benefit and added benefit of selpercatinib in advanced RET fusion-positive solid tumours. LIBRETTO-001 is an ongoing, uncontrolled, prospective basket study organized in 2 phases.

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 1st 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) [4] 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.

For the present therapeutic indication, adults with advanced RET fusion-positive solid tumours are relevant, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted. The company presented analyses on the 5st data cut-off from 24 September 2021 in Module 4 D of the dossier and used it for the benefit assessment. Up to this data cut-off, 806 patients were enrolled in the study and received at least 1 dose of selpercatinib. The company's analyses of this data cut-off include 45 patients from phase 1 and phase 2 of the study who were diagnosed with advanced RET fusion-positive solid tumours other than NSCLC and thyroid cancer, in whom the disease progressed during or after previous systemic therapy and for whom no satisfactory treatment options were available. In deviation from the SPC, 9 patients (20%) of this subpopulation were treated with a starting dose of 160 mg despite having a body weight below 50 kg.

In addition, in Appendix 4-M of Module 4 D, the company presented analyses of the most recent 6th data cut-off from 13 January 2023 for adult patients with solid tumours other than NSCLC and thyroid cancer (N = 55).

As the LIBRETTO-001 study did not provide a comparison with the G-BA's ACT, the study is not suitable for the benefit assessment.

I 4 Results on added benefit

No suitable data are available for the assessment of the additional benefit of selpercatinib in comparison with the ACT in patients with advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted. There is no hint of an added benefit of selpercatinib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Selpercatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with advanced RET fusion-positive solid tumours[b], when treatment options not targeting RET provide limited clinical benefit, or have been exhausted	Best supportive care[c]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. NSCLC and thyroid cancer are not covered by the present therapeutic indication. Separate therapeutic indications for selpercatinib exist for these two indications. c. 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; NSCLC: non-small cell lung 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 for selpercatinib based on the uncontrolled LIBRETTO-001 study.

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Subbiah V, Wolf J, Konda B et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol 2022; 23(10): 1261-1273. https://doi.org/10.1016/S1470-2045(22)00541-1.

4. Lilly. Retsevmo [online]. 2024 [Accessed: 14.06.2024]. URL: https://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-63.html.