Belzutifan
(von Hippel-Lindau disease)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Belzutifan (Von-Hippel-Lindau-Syndrom) – Nutzenbewertung gemäß § 35a SGB V*. 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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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 of persons concerned was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 belzutifan. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 March 2025.

Research question

The aim of this report is to assess the added benefit of belzutifan compared with watchful waiting as an appropriate comparator therapy (ACT) in adult patients with von Hippel-Lindau disease who require therapy for associated, localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of belzutifan

Therapeutic indication	**ACT**[a, b]
Adult patients with von Hippel-Lindau disease who require therapy for associated localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. For the determination of the ACT, the G-BA assumes that patients in the metastatic stage are not covered by the therapeutic indication. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's ACT.

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, no randomized controlled trial (RCT) on the direct comparison of belzutifan with the comparator therapy specified by the G-BA was identified. Therefore, the company conducted an information retrieval on further investigations with belzutifan and identified the single-arm study LITESPARK 004, on the basis of which the approval of belzutifan

was granted. The company conducted no information retrieval on further investigations with the ACT.

To derive the added benefit, the company used a descriptive comparison of the single-arm study LITESPARK 004 with retrospective data from the Von Hippel-Lindau Natural History Study.

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

Evidence provided by the company

On the intervention side, the company included the ongoing, open-label, single-arm study LITESPARK 004. The study included adult patients with confirmed Von Hippel-Lindau disease and at least 1 solid clear cell renal cell carcinoma. On the comparator side, the company used the retrospective, non-interventional Von Hippel-Lindau Natural History Study. The National Cancer Institute Urologic Oncology Branch Von-Hippel-Lindau Hereditary Database served as the data source. The study included patients with confirmed Von Hippel-Lindau disease and at least 1 solid renal tumour who were treated at the National Institutes of Health Clinical Center in Bethesda (USA).

The comparison of the two studies LITESPARK 004 and Von Hippel-Lindau Natural History Study presented by the company is purely descriptive (without calculation of effect estimates). Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies (such as the comparison of individual study arms), group differences in possible confounders, i.e. factors which are related to both the treatment and outcomes and can thus alter the estimation of the treatment effect, must be taken into account in the estimation. The company neither searched for potentially relevant confounders nor did it attempt to adjust for possible group differences. At the same time, the observed differences between the individual study arms with regard to the patient-relevant outcomes were not so large that they could not be explained by bias alone.

Irrespective of this, the treatment and observation durations vary greatly between the two studies (approx. 5 vs. approx. 10 years), so that the results cannot be meaningfully interpreted in the present situation, regardless of the lack of adjustment. In addition, no results on side effects were recorded on the comparator side, so that an overall assessment of potential effects across all outcome categories would not be possible.

Overall, the results presented by the company are unsuitable for assessing the added benefit of belzutifan in comparison with the ACT.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of belzutifan 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 belzutifan.

Table 3: Belzutifan – probability and extent of added benefit

Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adult patients with von Hippel-Lindau disease who require therapy for associated localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable	Watchful waiting	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. For the determination of the ACT, the G-BA assumes that patients in the metastatic stage are not covered by the therapeutic indication.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of belzutifan compared with watchful waiting as an ACT in adult patients with von Hippel-Lindau disease who require therapy for associated, localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable.

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

Table 4: Research question for the benefit assessment of belzutifan

Therapeutic indication	**ACT**[a, b]
Adult patients with von Hippel-Lindau disease who require therapy for associated localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. For the determination of the ACT, the G-BA assumes that patients in the metastatic stage are not covered by the therapeutic indication. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's ACT.

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- study list on belzutifan (status: 03 February 2025)
- bibliographical literature search on belzutifan (last search on 03 February 2025)
- search in trial registries/trial results databases for studies on belzutifan (last search on 03 February 2025)
- search on the G-BA website for belzutifan (last search on 03 February 2025)

To check the completeness of the study pool:

- search in trial registries for studies on belzutifan (last search on 14 April 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, no RCT on the direct comparison of belzutifan with the comparator therapy specified by the G-BA was identified. Therefore, the company conducted an information retrieval on further investigations with belzutifan and identified the single-arm study LITESPARK 004 [3], on the basis of which the approval of belzutifan was granted. The company conducted no information retrieval on further investigations with the ACT.

To derive the added benefit, the company used a descriptive comparison of the single-arm study LITESPARK 004 with retrospective data from the Von Hippel-Lindau Natural History Study [4].

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

Evidence provided by the company

On the intervention side, the company included the ongoing, open-label, single-arm study LITESPARK 004. The study included adult patients with confirmed Von Hippel-Lindau disease and at least 1 solid clear cell renal cell carcinoma. The prerequisite was that no clear cell renal cell carcinoma with a diameter greater than 3 cm requiring immediate surgical intervention was present at the time of screening. The patients could have other Von-Hippel-Lindau-associated tumours in other organs. All patients received belzutifan in the approved dosage of 120 mg once daily [5]. For the benefit assessment, the company used a data cut-off of 1 April 2024 with a median treatment and observation duration of approx. 5 years. Primary outcome was the objective response rate according to Response Evaluation Criteria in Solid

Tumours (RECIST) version 1.1. Secondary outcomes included other RECIST-based outcomes and outcomes on side effects.

On the comparator side, the company used the retrospective, non-interventional Von Hippel-Lindau Natural History Study. The National Cancer Institute Urologic Oncology Branch Von-Hippel-Lindau Hereditary Database served as the data source. The study included patients with confirmed Von Hippel-Lindau disease and at least 1 solid renal tumour who were treated at the National Institutes of Health Clinical Center in Bethesda (USA). Patients were not allowed to have received interventional therapy 30 days before or after the first radiological evidence of a solid renal tumour during the study period. The period considered was from 31 July 2004 to 30 June 2020. The median observation period of the patients was approx. 10 years. Primary outcome of the study was the tumour size. According to the information in Module 4 A, secondary outcomes included, for example, mortality and various RECIST-based outcomes.

The comparison of the two studies LITESPARK 004 and Von Hippel-Lindau Natural History Study presented by the company is purely descriptive (without calculation of effect estimates). Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies (such as the comparison of individual study arms), group differences in possible confounders, i.e. factors which are related to both the treatment and outcomes and can thus alter the estimation of the treatment effect, must be taken into account in the estimation. The company neither searched for potentially relevant confounders nor did it attempt to adjust for possible group differences. At the same time, the observed differences between the individual study arms with regard to the patient-relevant outcomes were not so large that they could not be explained by bias alone.

Irrespective of this, the treatment and observation durations vary greatly between the two studies (approx. 5 vs. approx. 10 years), so that the results cannot be meaningfully interpreted in the present situation, regardless of the lack of adjustment. In addition, no results on side effects were recorded on the comparator side, so that an overall assessment of potential effects across all outcome categories would not be possible.

Overall, the results presented by the company are unsuitable for assessing the added benefit of belzutifan in comparison with the ACT.

I 4 Results on added benefit

There are no suitable data for the assessment of the added benefit of belzutifan compared with watchful waiting in adult patients with von Hippel-Lindau disease who require therapy for associated, localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable. There is no hint of an added benefit of belzutifan in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of belzutifan in comparison with the ACT is summarized in Table 5.

Table 5: Belzutifan – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adult patients with von Hippel-Lindau disease who require therapy for associated localized renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localized procedures are unsuitable	Watchful waiting	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. For the determination of the ACT, the G-BA assumes that patients in the metastatic stage are not covered by the therapeutic indication.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit based on a descriptive comparison of two single-arm studies.

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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