Belzutifan
(renal cell carcinoma)

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 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
AE	adverse event
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KPS	Karnofsky Performance Status
PD(L) 1	programmed cell death ligand 1
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SmPC	Summary of Product Characteristics
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

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 28 March 2025.

Research question

The aim of this report is to assess the added benefit of belzutifan compared with individualized treatment as an appropriate comparator therapy (ACT) in adult patients with advanced clear cell renal cell carcinoma that has progressed following 2 or more therapies that included a Programmed Cell Death-(Ligand) 1 (PD [L] 1) inhibitor and at least 2 vascular endothelial growth factor targeted therapies.

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 advanced clear cell renal cell carcinoma that has progressed following 2 or more lines of therapy that included a PD-(L)1 inhibitor and at least 2 vascular endothelial growth factor-targeted therapies	Individualized treatment[c, d, e] choosing from ▪ axitinib, ▪ cabozantinib, ▪ everolimus, ▪ lenvatinib in combination with everolimus and ▪ sunitinib

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the treatment decision and that treatment is palliative.
c. The treatment decision is made under particular consideration of the prior therapy. When choosing the treatment option, a change of the tyrosinkinase inhibitor (TKI) must be made with regard to the previously administered TKI.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria.
e. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).

ACT: appropriate comparator therapy G-BA: Federal Joint Committee; PD-(L)1: Programmed Cell Death Protein-(Ligand) 1; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

The company followed the ACT specified by the G-BA.

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

Randomized controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The RCT LITESPARK 005 was included in this benefit assessment. This study is an ongoing, open-label RCT comparing belzutifan with everolimus. Accordingly, the study was not designed for a comparison with individualized treatment, as defined by the G-BA as an ACT. However, with certain restrictions, the study is suitable for such a comparison (see below).

The LITESPARK 005 study included adult patients with unresectable, locally advanced or metastatic clear cell renal cell carcinoma and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Patients had to have radiological evidence of disease progression after or during sequential or combined therapy with one PD-(L)1 inhibitor and one vascular endothelial growth factor (VEGF)-targeted therapy. Furthermore, patients were not allowed to have metastases in the central nervous system and had to be in good general health (Karnofsky Performance Status [KPS] ≥ 70 %).

The LITESPARK 005 study included a total of 746 patients, randomized in a 1:1 ratio either to treatment with belzutifan (N = 374) or everolimus (N = 372). Randomization was stratified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category (favourable vs. intermediate vs. poor) and the number of previous VEGF-targeted therapies (1 vs. 2 to 3). Only the subpopulation of patients with 2 or more prior therapies who were treated with one PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies is relevant for the present benefit assessment. It included 188 patients in the intervention arm and 182 in the comparator arm. The company presented results for this subpopulation in the dossier. These are used for the benefit assessment.

Treatment with belzutifan in the intervention arm and with everolimus in the comparator arm was largely in compliance with the specifications of the respective Summary of Product Characteristics (SmPC). The study did not provide for any switching between study arms.

Co-primary outcomes of the LITESPARK 005 study were overall survival and progression-free survival. Patient-relevant secondary outcomes comprised outcomes in the categories morbidity, health-related quality of life and side effects.

Implementation of the ACT

The G-BA defined an individualized treatment choosing from axitinib, cabozantinib, everolimus, lenvatinib in combination with everolimus and sunitinib as the ACT. The treatment decision is to be made under particular consideration of the prior therapy. In its notes on the

ACT, the G-BA further describes that for the implementation of the individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study).

All patients in the comparator arm of the LITESPARK 005 study received treatment with everolimus. The other treatment options covered by the ACT were not available, so individualized treatment taking into account the prior therapy was not possible within the scope of the study.

In accordance with the market authorization, belzutifan can be used from the third-line therapy of advanced renal cell carcinoma. In the LITESPARK 005 study, 17% of the patients in the subpopulation presented in the dossier were undergoing third-line treatment and 81% of the patients were undergoing fourth-line treatment. For patients with advanced and/or metastatic clear cell renal cell carcinoma, there is no established standard of care for these treatment lines from national and international guidelines.

Based on the guideline recommendations, the choice of therapy in the late lines of treatment is primarily based on which drugs have already been used in the previous lines of treatment. According to the inclusion criteria, the patients in the LITESPARK 005 study had not used everolimus or another drug with the same mechanism of action in the previous therapy, which is why it can be assumed that everolimus is generally a suitable treatment option for all patients. Information on the drugs used in the previous lines of treatment is required in order to be able to estimate for how many patients an individualized treatment with one of the other options axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib covered by the ACT would also have been suitable. However, the company’s dossier does not provide these data for the relevant subpopulation. The analyses of the total population show that 51% of patients received cabozantinib, 41% sunitinib, 28% axitinib and 2% lenvatinib as part of their prior therapy. It can be assumed that the proportions in the subpopulation tend to be higher because it exclusively comprises patients with ≥ 2 previous lines of treatment. Based on the information on prior therapies, it can be assumed that a combination therapy of lenvatinib and everolimus would have been an option for the majority of patients in addition to everolimus. Due to the lack of further criteria for the treatment decision, it is unclear for how many patients combination therapy might have been a more suitable treatment option.

Overall, the LITESPARK 005 study was used for the benefit assessment in the present situation despite the uncertainties described. It is assumed that treatment with everolimus represents a sufficient implementation of an individualized treatment taking into account the prior treatment, as the patients included in the study had not yet received the drug in their pretreatment and further criteria for the treatment decision are missing. However, it is unclear whether other treatment options included in the G-BA's ACT would also have been

suitable or even more suitable for some of the patients. This uncertainty is taken into account in the assessment of the certainty of results.

Based on the results of the LITESPARK 005 study, conclusions on the added benefit of belzutifan can only be made for those patients for whom treatment with everolimus is the suitable individualized treatment.

Available data cut-offs

Three data cut-offs are currently available for the LITESPARK 005 study. Concurring with the company's approach, the analyses on the final data cut-off (15 April 2024) were used for the benefit assessment.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for the LITESPARK 005 study.

There was a low risk of bias for the results of the outcome overall survival. The results on morbidity and health-related quality of life, recorded using the instruments European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms (FKSI-DRS) and the EQ-5D visual analogue scale (VAS) have a high risk of bias. One reason for this is the lack of blinding, as the outcomes are recorded subjectively by the patients. Furthermore, the proportion of missing questionnaires for potentially informative reasons increased sharply over the course of the study and differed between the treatment arms.

The risk of bias for the results of the outcome discontinuation due to AEs was high because of the unblinded study design in the presence of subjective decision on treatment discontinuation. For the other results in the side effects category, the high risk of bias was due to the shortened observations for potentially informative reasons. In addition, the unblinded study design leads to a high risk of bias in the non-severe/non-serious side effects due to the subjective recording of outcomes.

Irrespective of the aspects listed under the risk of bias, the certainty of conclusions of the results from the LITESPARK 005 study is reduced across all outcomes. The reason for this is that, due to the uncertainties described above, it cannot be ruled out that another treatment option included in the G-BA's ACT would have been more suitable for some of the patients included. It therefore remains unclear whether the results of the study can be transferred to the German health care context without restriction. Based on the LITESPARK 005 study, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

No statistically significant difference between the treatment arms was shown for the scales fatigue, nausea and vomiting, dyspnoea and constipation. In each case, there was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

A statistically significant effect in favour of belzutifan in comparison with everolimus was shown for each of the scales insomnia, appetite loss and diarrhoea. In each case, this results in a hint of an added benefit of belzutifan in comparison with everolimus.

There is a statistically significant difference between the treatment arms for the pain scale, but the extent of the effect is no more than minor. However, there is an effect modification for the characteristic age. There is a hint of an added benefit of belzutifan in comparison with everolimus for patients aged ≥ 65 years. For patients < 65 years, there is no hint of an added benefit of belzutifan compared to everolimus; an added benefit is therefore not proven.

FKSI-DRS

A statistically significant effect in favour of belzutifan in comparison with everolimus was shown for the outcome symptoms, recorded with the FKSI-DRS. The extent of the effect was no more than marginal, however. There was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome health status, recorded with the EQ-5D VAS. There was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning)

No statistically significant difference between the treatment arms was found for any of the scales global health status, role functioning, emotional functioning and cognitive functioning of the EORTC QLQ-C30. In each case, there was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

There was no statistically significant difference between the treatment arms for the physical functioning scale. However, there is an effect modification for the characteristic IMDC risk category. For patients with a poor IMDC risk category, there is a hint of an added benefit of belzutifan over everolimus. For patients with a favourable or intermediate IMDC risk category, there is no hint of an added benefit of belzutifan over everolimus; an added benefit is therefore not proven for this patient group.

No statistically significant difference between the treatment arms was found for the social functioning scale. However, there is an effect modification for the characteristic age. For patients ≥ 65 years, there is a hint of an added benefit of belzutifan over everolimus. For patients < 65 years, there is no hint of an added benefit of belzutifan over everolimus; an added benefit is therefore not proven for this patient group.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

There is no statistically significant difference between the treatment arms for the outcome severe AEs. There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference in favour of belzutifan compared with everolimus was shown for the outcome discontinuation due to AEs. However, there is an effect modification for the characteristic age. There is a hint of lesser harm from belzutifan in comparison with everolimus for patients aged ≥ 65 years. For patients < 65 years, there was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Specific AEs

Hypoxia (PT, severe AEs)

For the outcome hypoxia (PT, severe AEs), a statistically significant difference was found to the disadvantage of belzutifan in comparison with everolimus. There is a hint of greater harm from belzutifan in comparison with everolimus.

Anaemia (PT, severe AEs)

No statistically significant difference between the treatment arms was found for the outcome anaemia (PT, severe AEs). There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Pneumonitis (PT, severe AEs)

No suitable data are available for the outcome pneumonitis (PT, severe AEs). There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Infections and infestations (SOC, severe AEs)

A statistically significant difference in favour of belzutifan compared with everolimus was shown for the outcome infections and infestations (SOC, severe AEs). There is a hint of lesser harm from belzutifan in comparison with everolimus.

Further specific AEs - constipation (PT, AEs), stomatitis (PT, AEs), fever (PT, AEs), dizziness (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), fatigue (PT, severe AEs) and hyperglycaemia (PT, severe AEs)

For each of the outcomes stomatitis (PT, AEs), fever (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), fatigue (PT, severe AEs) and hyperglycaemia (PT, severe AEs), there was a statistically significant difference in favour of belzutifan compared to everolimus. In each case, there is a hint of lesser harm from belzutifan in comparison with everolimus.

For each of the outcomes constipation (PT, AEs) and dizziness (PT, AEs), a statistically significant difference was found to the disadvantage of belzutifan in comparison with everolimus. There is a hint of greater harm from belzutifan in comparison with everolimus in each case.

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

On the basis of the results presented, the probability and extent of added benefit of the drug belzutifan in comparison with the ACT is assessed as follows:

Patients for whom everolimus is a suitable individualized treatment

Overall, both positive and negative effects of belzutifan were found in comparison with the ACT. The characteristics age and IMDC risk category are effect modifiers for several outcomes. Due to the effect modification by the characteristic age both for individual outcomes of symptoms and health-related quality of life (EORTC QLQ-C30) and for the outcome discontinuation due to AEs, the results on the added benefit of belzutifan compared with the ACT are derived separately below:

Patients aged ≥ 65 years

On the positive effects side, there are hints of an added benefit, in some cases with considerable extent, for several symptom scales recorded using the EORTC QLQ-C30. There are further positive effects in the side effects category for several specific AEs of different severity categories, each with considerable or major extent.

For patients ≥ 65 years, there are also hints of a considerable added benefit for the pain scale of the EORTC QLQ-C30 and for the outcome discontinuation due to AEs. In addition, there is a hint of major added benefit for this patient group in health-related quality of life for one scale (social functioning of the EORTC QLQ-C30).

On the other hand, there are negative effects for specific AEs in the side effects category of varying severity categories and with varying, partly major extent. Overall, these negative effects are not assumed to completely call into question the partially major effects in patients ≥ 65 years.

In summary, for adult patients ≥ 65 years of age with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies, and for whom everolimus is a suitable individualized treatment, there is a hint of considerable added benefit of belzutifan compared with the ACT.

[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].

Patients < 65 years

Analogous to patients ≥ 65, various positive effects were also shown for patients aged < 65 years for several symptom outcome scales (EORTC QLQ-C30) and for some specific AEs of different severity categories. For patients < 65 years, however, there were no effects on health-related quality of life or discontinuation due to AEs. On the other hand, there are negative effects for specific AEs of varying severity categories, some of them with major extent.

In summary, for adult patients < 65 years of age with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies, and for whom everolimus is a suitable individualized treatment, there is a hint of minor added benefit of belzutifan compared with the ACT.

Patients for whom everolimus is no suitable individualized treatment

For adult patients with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies, and for whom everolimus is not a suitable individualized treatment, there are no data for the assessment of the added benefit of belzutifan over the ACT from LITESPARK 005. An added benefit is therefore not proven for this patient group.

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 advanced clear cell renal cell carcinoma that has progressed following 2 or more therapies that included a PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies	Individualized treatment[c, d, e] choosing from ▪ axitinib, ▪ cabozantinib, ▪ everolimus, ▪ lenvatinib in combination with everolimus and ▪ sunitinib	▪ Patients for whom everolimus is a suitable individualized treatment[f]: ▫ < 65 years: hint of minor added benefit ▫ ≥ 65 years: hint of considerable added benefit ▪ patients for whom everolimus is not a suitable individualized treatment: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the treatment decision and that treatment is palliative.
c. The treatment decision is made under particular consideration of the prior therapy. When choosing the treatment option, a change of the tyrosinkinase inhibitor (TKI) must be made with regard to the previously administered TKI.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria.
e. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
f. The LITESPARK 005 study included only patients with a Karnofsky performance status ≥ 70 %. It remains unclear whether the observed effects can be transferred to patients with a Karnofsky performance status < 70 %.

ACT: appropriate comparator therapy G-BA: Federal Joint Committee; PD-(L)1: Programmed Cell Death Protein-(Ligand) 1; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of belzutifan compared with individualized treatment as an ACT in adult patients with advanced clear cell renal cell carcinoma that has progressed following 2 or more therapies that included a PD (L) 1 inhibitor and at least 2 vascular endothelial growth factor targeted therapies.

The research question shown in Table 4 was defined in accordance with 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 advanced clear cell renal cell carcinoma that has progressed following 2 or more lines of therapy that included a PD-(L)1 inhibitor and at least 2 vascular endothelial growth factor-targeted therapies	Individualized treatment[c, d, e] choosing from ▪ axitinib, ▪ cabozantinib, ▪ everolimus, ▪ lenvatinib in combination with everolimus and ▪ sunitinib
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the treatment decision and that treatment is palliative. c. The treatment decision is made under particular consideration of the prior therapy. When choosing the treatment option, a change of the tyrosinkinase inhibitor (TKI) must be made with regard to the previously administered TKI. d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria. e. The term “individualized treatment” is used instead of previously used terms such as “patient-specific therapy” or “treatment of physician’s choice”. This ensures consistency with the terms used in European health technology assessments (EU HTAs). ACT: appropriate comparator therapy G-BA: Federal Joint Committee; PD-(L)1: Programmed Cell Death Protein-(Ligand) 1; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor	

The company followed the ACT specified by the G-BA.

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

RCTs were used to derive the added benefit. This concurred with the company’s inclusion criteria.

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

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: belzutifan vs. everolimus

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
LITESPARK 005	Yes	Yes	No	Yes [3-5]	Yes [6-8]	Yes [9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial

The RCT LITESPARK 005 was included in this benefit assessment. The study compares belzutifan with everolimus. Accordingly, the study was not designed for a comparison with individualized treatment, as defined by the G-BA as an ACT. However, with certain restrictions, the study is suitable for such a comparison (see Section I 3.2).

The study pool was consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the LITESPARK 005 study for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LITESPARK 005	RCT, open-label, parallel	Patients (≥ 18 years) ▪ with non-resectable, locally advanced or metastatic clear cell renal cell carcinoma[b, c] ▪ progressive after or during sequential or combined therapy with PD-(L)1 inhibitor and VEGF-targeted therapy[d, e] ▪ Karnofsky performance status ≥ 70%[f]	Belzutifan (N = 374) everolimus (N = 372) relevant subpopulation thereof[g]: belzutifan (N = 188) everolimus (N = 182)	Screening: up to 28 days treatment: until disease progression[h], unacceptable toxicity or decision by the investigator or the patient observation[i]: outcome-specific, at most until death, withdrawal of consent or end of the study	147 study centres in Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Italy, Japan, Norway, Republic of Korea, Russia, Spain, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, USA 02/2020–ongoing data cut-offs: 1 November 2022[j] 13 June 2023[k] 15 April 2024[l]	Coprimary: PFS, overall survival secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Measurable according to RECIST version 1.1. Lesions in a previously irradiated area are considered measurable if there is proof of progression in these lesions.
c. Patients with metastases in the central nervous system and/or meningeosis carcinomatosa were excluded.
d. Patients had to have received ≥ 2 doses of a PD-(L)1 inhibitor.
e. Pretreated with ≤ 3 systemic therapy regimens for locally advanced or metastaticrenal cell carcinoma and with radiological progression of the disease following the last therapy.
f. ≤ 10 days before randomization.
g. Patients who had already received 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies.
h. Confirmed by blinded independent central review (BICR). Continuation of treatment beyond BICR-confirmed radiological disease progression according to RECIST 1.1 requires the consent of the sponsor. If treatment is continued beyond confirmed disease progression, all investigations prescribed in the protocol must be carried out.
i. Outcome-specific information is provided in Table 8.
j. Interim analysis 1, from Amendment 6 of the study protocol (13 July 2022) planned after the occurrence of 563 PFS events and after an observation period for all patients of approx. 7 months.
k. Interim analysis 2, from Amendment 6 of the study protocol (13 July 2022) planned after the occurrence of 410 deaths and after an observation period for all patients of approx. 17 months.
l. Final analysis, planned from Amendment 6 of the study protocol (13 July 2022) after the occurrence of 483 deaths and after an observation period of all patients of approx. 27 months.

AE: adverse event; BICR: blinded independent central review; n: relevant subpopulation; N: number of randomized (included) patients; PD-(L)1: programmed cell death (ligand) 1; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; VEGF: vascular endothelial growth factor

Table 7: Characteristics of the intervention – RCT, direct comparison: belzutifan vs. everolimus

Study	Intervention	Comparison
LITESPARK 005	Belzutifan 120 mg once daily, oral	Everolimus 10 mg once daily, oral
	Dose adjustment: ▪ dose reduction[a] and/or interruption permitted in case of toxicity[b]	▪ Dose adjustments allowed according to the SmPC
	Disallowed pretreatment ▪ belzutifan/other HIF-2α inhibitors ▪ everolimus/other TORC1/PI3K/AKT inhibitors in advanced-stage disease ▪ > 3 systemic therapies for locally advanced or metastatic renal cell carcinoma **concomitant treatment** ▪ any treatments necessary for the patient's wellbeing. **disallowed concomitant treatment** ▪ antineoplastic systemic chemotherapies or biologic therapies ▪ therapies with low molecular kinase inhibitors, radiotherapy[c] (≤ 2 weeks before randomization), systemic antibodies (≤ 4 weeks before randomization) ▪ major surgery (≤ 3 weeks before randomization) ▪ therapy with colony-stimulating factors (≤ 28 days before randomization) ▪ live vaccines (≤ 30 days before randomization) ▪ systemic glucocorticoids for any purpose other than the treatment of side effects[d] ▪ strong CYP3A4 inhibitors[e] ▪ ACE inhibitors[f] ▪ other investigational preparations	

a. After interruption of therapy due to toxicity, a reduction of the starting dose to 80 mg (level –1) or 40 mg (level –2) is permitted once daily. At dose level –2 at the latest, treatment must be discontinued if toxicity occurs again. Re-escalation of the dose to the next higher level is permitted after consultation with the sponsor in patients who have resumed treatment with belzutifan for ≥ 28 days and no new toxicity has occurred. Re-escalation was not permitted in case of grade ≥ 3 symptomatic hypoxia.
b. In the event of an interruption > 28 days, the sponsor must be consulted.
c. Palliative radiotherapy to treat symptomatic lesions or the brain is permitted. For inclusion in the study, patients must have recovered from all toxicities due to radiotherapy and there must be no need for treatment with corticosteroids.
d. Corticosteroid replacement therapy for pituitary or adrenal insufficiency as well as inhaled, intranasal, ophthalmological, intra-articular or intrathecal steroid injections are permitted.
e. For patients in the belzutifan arm, treatment with moderate CYP3A4 inhibitors or moderate/strong CYP3A4 inducers is only permitted after consultation with the sponsor; for patients in the everolimus arm, treatment is carried out in accordance with the SmPC.
f. Only for patients in the everolimus arm. Intake is permitted for patients in the belzutifan arm.

ACE: angiotensin-converting enzyme; AKT: AK strain transforming (protein kinase B); CYP3A4: cytochrome P450 3A4; HIF: hypoxia-inducible factor; PI3K: phosphoinositide 3-kinase; RCT: randomized controlled trial; TORC1: target of rapamycin complex 1

This LITESPARK 005 study is an ongoing, open-label RCT comparing belzutifan with everolimus. It included adult patients with unresectable, locally advanced or metastatic clear cell renal cell carcinoma and measurable disease according to RECIST 1.1. Patients had to have radiological

evidence of disease progression after or during sequential or combined therapy with 1 PD-(L)1 inhibitor and 1 VEGF-targeted therapy. Furthermore, patients were not allowed to have metastases in the central nervous system and had to be in good general health (KPS ≥ 70 %).

The LITESPARK 005 study included a total of 746 patients, randomized in a 1:1 ratio either to treatment with belzutifan (N = 374) or everolimus (N = 372). Randomization was stratified according to the IMDC risk category (favourable vs. intermediate vs. poor) and the number of previous VEGF-targeted therapies (1 vs. 2 to 3). Only the subpopulation of patients with 2 or more prior therapies who were treated with one PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies is relevant for the present benefit assessment. It included 188 patients in the intervention arm and 182 in the comparator arm. The company presented results for this subpopulation in the dossier. These are used for the benefit assessment.

Treatment with belzutifan in the intervention arm and with everolimus in the comparator arm was largely in compliance with the specifications of the respective SmPC [10,11]. According to the SmPC, treatment with belzutifan should be continued until the disease progresses. However, if radiological progression occurs in the study, treatment may be continued at the discretion of the investigator with the consent of the sponsor. It is unclear how many patients in the subpopulation continued treatment with belzutifan after disease progression. The deviation from the SmPC has no consequences for the benefit assessment. The study did not provide for any switching between study arms.

Co-primary outcomes of the LITESPARK 005 study were overall survival and progression-free survival. Patient-relevant secondary outcomes comprised outcomes in the categories morbidity, health-related quality of life and side effects.

Implementation of the ACT

The G-BA defined an individualized treatment choosing from axitinib, cabozantinib, everolimus, lenvatinib in combination with everolimus and sunitinib as the ACT. The treatment decision is to be made under particular consideration of the prior therapy. In its notes on the ACT, the G-BA further describes that for the implementation of the individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). A rationale had to be provided for the choice and any limitation of treatment options.

All patients in the comparator arm of the LITESPARK 005 study received treatment with everolimus. The other treatment options covered by the ACT were not available, so individualized treatment taking into account the prior therapy was not possible within the scope of the study. In the company's opinion, the implementation of the ACT in the LITESPARK 005 study was adequate, as everolimus was a drug not yet used in the previous therapy with

a target structure that had not yet been addressed. This was based on the inclusion criteria of the study, according to which the patients were not allowed to have previously received everolimus or any other specific or selective target of rapamycin complex 1, phosphoinositide 3-kinase or protein kinase B inhibitor for the treatment of advanced clear cell renal cell carcinoma. The company does not justify the restriction of the treatment options to everolimus in the study. It also provides no further information on why everolimus is the most appropriate therapy for the patients included.

In accordance with the market authorization [10], belzutifan can be used from the third-line therapy of advanced renal cell carcinoma. In the LITESPARK 005 study, 17% of the patients in the subpopulation presented in the dossier were undergoing third-line treatment, and 81% of the patients were already undergoing fourth-line treatment. For patients with advanced and/or metastatic clear cell renal cell carcinoma, there is no established standard of care for these treatment lines from national and international guidelines [12-14]. According to the current S3 guideline "Diagnosis, treatment and follow-up of renal cell carcinoma", previous therapies should be taken into account when selecting the third-line therapy and substances should be administered that were not part of the previous therapy [12]. In addition to belzutifan, the current European Society for Medical Oncology Clinical Practice Guideline for renal cell carcinoma recommends the use of a VEGF-targeted therapy which has not been administered before from third-line treatment onwards. Treatment with everolimus should be considered if the previously mentioned options are not available [13]. Apart from the previous therapy, the guidelines do not specify any other criteria that should be taken into account when deciding on treatment.

Based on the guideline recommendations, the choice of therapy in the late lines of treatment is primarily based on which drugs have already been used in the previous lines of treatment. In the patients included in the LITESPARK 005 study, neither everolimus nor any other drug with the same mechanism of action was used in prior therapy, which is why it can be assumed that everolimus is a suitable treatment option for all patients. Information on the drugs used in the previous lines of treatment is required in order to be able to estimate for how many patients an individualized treatment with one of the other options axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib covered by the ACT would also have been suitable. However, the company’s dossier does not provide these data for the relevant subpopulation. The analyses of the total population show that 51% of patients received cabozantinib, 41% sunitinib, 28% axitinib and 2% lenvatinib as part of their prior therapy. It can be assumed that these proportions are higher in the subpopulation because this exclusively comprises the part of the study population of patients who were more heavily pretreated (≥ 2 previous treatment lines). However, based on the information on prior therapies, it can be assumed that in particular a combination therapy of lenvatinib and everolimus would have been an option for the majority of patients besides everolimus. Due

to the lack of further criteria for the treatment decision, it is unclear for how many patients combination therapy might have been a more suitable treatment option.

Overall, the LITESPARK 005 study was used for the benefit assessment in the present situation despite the uncertainties described. It is assumed that treatment with everolimus represents a sufficient implementation of an individualized treatment taking into account the prior therapy, as the already extensively pretreated patients included in the study had not yet received the drug in their pretreatment and, moreover, further criteria for the treatment decision are missing. However, it is unclear whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable for some of the patients. This uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2).

Based on the results of the LITESPARK 005 study, conclusions on the added benefit of belzutifan can only be made for those patients for whom treatment with everolimus is the suitable individualized treatment.

Available data cut-offs

For the LITESPARK 005 study, the original planning of the data cut-offs was adjusted with Amendment 6 of the study protocol (13 July 2022), partly because recruitment took longer than expected. The following 3 data cut-offs are available:

- 1 November 2022 (interim analysis 1; planned after the occurrence of 563 PFS events and after an observation period of approx. 7 months for all patients)
- 13 June 2023 (interim analysis 2; planned after the occurrence of 410 deaths and after an observation period for all patients of approx. 17 months for all patients.
- 15 April 2024; (final analysis, planned after the occurrence of 483 deaths and after an observation period of approx. 27 months for all patients)

Concurring with the company’s approach, the analyses on the final data cut-off (15 April 2024) were used for the benefit assessment.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: belzutifan vs. everolimus

Study **outcome category** **outcome**	**Planned follow-up observation**
LITESPARK 005	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study, whichever is first
Morbidity	
Symptoms (EORTC QLQ-C30, FKSI-DRS)	Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30	Until 30 days after the last dose of the study medication
Side effects	
AEs, severe AEs[a]	Up to 30 days after the last dose of the study medication or before the start of a new treatment
SAEs	Up to 90 days after the last dose of the study medication or up to 30 days after the last dose of the study medication when starting a new therapy

a. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days or 90 days). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study characteristic category	**Belzutifan N = 188**	**Everolimus N = 182**
LITESPARK 005		
Age [years], mean (SD)	62 (9)	63 (10)
Sex [F/M], %	21/79	21/79
Region, n (%)		
North America	46 (25)	39 (21)
Western Europe	104 (55)	99 (54)
Rest of the world	38 (20)	44 (24)
Karnofsky performance status, n (%)		
70/80	71 (38)	69 (38)
90/100	117 (62)	113 (62)
IMDC risk category, n (%)		
Favourable	42 (22)	42 (23)
Intermediate	123 (65)	120 (66)
Poor	23 (12)	20 (11)
Number of organs affected at baseline, n (%)		
1	15 (8)	11 (6)
≥ 2	173 (92)	171 (94)
Prior oncologic radiotherapy n (%)		
Yes	82 (44)	89 (49)
No	106 (56)	93 (51)
Prior nephrectomy, n (%)		
Yes	144 (77)	132 (73)
No	44 (23)	50 (27)
Number of prior lines of treatment, n (%)		
2	28 (15)	36 (20)
3	158 (84)	142 (78)
4[a]	2 (1)	4 (2)
Treatment discontinuation, n (%)[b]	157 (84)	176 (99)
Study discontinuation, n (%)[c]	128 (68)	125 (69)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study characteristic category	Belzutifan N = 188	Everolimus N = 182
a. According to the inclusion criteria, patients were not allowed to have received more than 3 prior systemic therapies for locally advanced or metastatic renal cell carcinoma. b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were the following (percentages based on randomized patients): AEs (7 % vs. 14 %), disease progression (64% vs. 69%), clinical progression (8% versus 8%). An additional 1% vs. 3% of randomized patients never started treatment. c. The data also comprise patients who died during the course of the study (percentages refer to randomized patients; intervention arm: 65% vs. control arm: 69%). Further reasons for study discontinuation in the intervention vs. control arm were: withdrawal of consent (3% vs. < 1%), investigator's decision (0% vs. < 1%). IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; f: female; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation		

The two treatment arms were balanced in terms of patients' demographic and clinical characteristics. The mean age of the patients was 62 and 63 years, and the majority (79%) were male. The majority of patients belonged to the intermediate IMDC risk category.

Most of them were patients who were already in the 4th line of treatment (84% of patients in the intervention arm vs. 78% in the comparator arm), while the study included only a small proportion of patients in the third line (15% vs. 20%).

Treatment discontinuation occurred in 99% of patients in the comparator arm and was thus higher than in the intervention arm, for which the proportion was 84%. The most common reasons were disease progression or discontinuation due to AEs. The proportion of patients who discontinued the study was comparable in both study arms (68% in the belzutifan arm and 69% in the everolimus arm; these figures include 65% vs. 69% of patients who died).

Information on the course of the study

Table 10 shows patients' median treatment duration and the median observation period for individual outcomes. Data on the mean treatment or observation periods are not available.

Table 10: Information on the course of the study – RCT, direct comparison: belzutifan vs. everolimus

Study **duration of the study phase** **outcome category/outcome**	**Belzutifan** **N = 188**	**Everolimus** **N = 182**
LITESPARK 005		
Treatment duration [months]		
Median [min; max]	7.2 [ND]	3.7 [ND]
Observation period [months]		
Overall survival[a]		
Median [min; max]	21.8 [ND]	18.1 [ND]
Morbidity		
Symptoms (EORTC QLQ-C30)		
Median [min; max]	7.0 [ND]	3.8 [ND]
Symptoms (FKSI-DRS)		
Median [min; max]	7.0 [ND]	3.7 [ND]
Health status (EQ-5D VAS)		
Median [min; max]	6.9 [ND]	3.8 [ND]
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	7.0 [ND]	3.8 [ND]
Side effects		
AEs		
Median [min; max]	8.2 [ND]	4.7 [ND]
SAEs		
Median [min; max]	9.6 [ND]	6.1 [ND]
Severe AEs (CTCAE grade ≥ 3)	ND	ND

a. Information on how the observation period was calculated is not available.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; max: maximum; min: minimum; N: number of randomized patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

In the LITESPARK 005 study, the median treatment duration was notably longer in the intervention arm, at 7.2 months, than in the comparator arm, at 3.7 months.

At the final data cut-off, the observation period for the outcome overall survival was 21.8 months in the intervention arm and 18.1 months in the comparator arm.

The median observation periods for the outcomes of the categories morbidity, health-related quality of life and side effects are significantly shortened compared to the outcome overall survival. In line with the planned observation until the last dose of study medication (plus 30

days or 90 days), the median observation period for these outcomes is also clearly longer in the intervention arm than in the comparator arm. For the patient-reported outcomes, it is noticeable that the planned follow-up duration of 30 days after the last dose of study medication is not reflected in the median observation period. This can probably be explained by the decline in response rates early in the course of the study.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent therapies (≥ 1% of the patients in ≥ 1 treatment arm)a – RCT, direct comparison: belzutifan vs. everolimus

Study drug class[b] drug	Patients with subsequent therapy, n (%)	
	intervention N = 188	comparison N = 182
LITESPARK 005		
Total[c]	100 (53.2)	124 (68.1)
First subsequent therapy: radiotherapy	16 (8.5)	5 (2.7)
First subsequent therapy: systemic therapy	84 (44.7)	119 (65.4)
Multiple	29 (15.4)	27 (14.8)
Everolimus	27 (14.4)	22 (12.1)
Other antineoplastic agents	1 (0.5)	5 (2.7)
Belzutifan	1 (0.5)	5 (2.7)
Other monoclonal antibodies and antibody drug conjugates	4 (2.1)	1 (0.5)
Ipilimumab	4 (2.1)	1 (0.5)
Other protein kinase inhibitors	43 (22.9)	61 (33.5)
Lenvatinib	19 (10.1)	24 (13.2)
Cabozantinib	12 (6.4)	17 (9.3)
Sunitinib	3 (1.6)	6 (3.3)
Cabozantinib S-malate	1 (0.5)	7 (3.8)
Sorafenib	3 (1.6)	3 (1.6)
Lenvatinib mesilate	3 (1.6)	1 (0.5)
Sunitinib malate	2 (1.1)	1 (0.5)
PD-1/PDL-1 inhibitors	12 (6.4)	15 (8.2)
Pembrolizumab	4 (2.1)	10 (5.5)
Nivolumab	8 (4.3)	5 (2.7)
VEGF tyrosine kinase inhibitors	16 (8.5)	29 (15.9)
Axitinib	15 (8.0)	25 (13.7)
Tivozanib	1 (0.5)	4 (2.2)

a. According to the company's information in Module4A, the first subsequent therapy includes both the first component of the subsequent therapy and the next component if this was administered within one week.
b. If several systemic therapies were administered in one therapy class, patients were only counted once in this class.
c. Institute's calculations.

n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

According to the study protocol, the choice of the subsequent therapy was not restricted. In the intervention arm, 53.2% of patients in the subpopulation received at least 1 subsequent therapy, compared to 68.1% in the comparator arm. In terms of patients who discontinued

treatment, 36% and 30% respectively did not receive any subsequent therapy. However, it is unclear for how many of the patients who discontinued treatment subsequent therapy was actually indicated (reasons for discontinuation were disease progression [64% vs. 69%], adverse events (AEs) [7% vs. 14%] and clinical progression [8% each], see Table 9).

The majority of patients received systemic therapy as the first subsequent therapy. The proportions of the administered drugs were largely comparable between the treatment arms. The most commonly used drugs were everolimus (14.4% vs. 12.1%), lenvatinib (10.1% vs. 13.2%), axitinib (8.0% vs. 13.7%) and cabozantinib (6.4% vs. 9.3%). 8.5% of the patients in the intervention arm and 2.7% of the patients in the comparator arm received radiotherapy.

At the time of the subsequent therapies, the patients were at least in the fourth line of treatment (83% in the fifth or sixth line of treatment), for which there is no therapy standard [12-14]. In the comparator arm, 12.1% received everolimus again in the subsequent therapy and thus did not receive a drug that had not yet been included in the previous therapy. However, it cannot be derived from the available information whether everolimus should be used as monotherapy or in combination with e.g. lenvatinib.

Overall, there are no indications that the subsequent therapies deviate to a relevant extent from the guideline recommendations.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: belzutifan versus everolimus

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
LITESPARK 005	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the LITESPARK 005 study.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

According to the company, the LITESPARK 005 study results can be transferred to the German health care context due to the characteristics of the investigated patient population, the study design, and the on-label use of belzutifan.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 4.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded using the EORTC QLQ-C30 and the FKSI-DRS
  - health status (EQ-5D VAS)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - hypoxia (PT, severe AEs)
  - anaemia (PT, severe AEs)
  - pneumonitis (PT, severe AEs)
  - infections and infestations (SOC, severe AEs)
  - other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: belzutifan vs. everolimus

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30, FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Hypoxia (PT, severe AEs[a])	Anaemia (PT, severe AEs)[a]	Pneumonitis (PT, severe AEs)[a]	Infections and infestations (SOC, severe AEs)[a]	Other specific AEs[b]
LITESPARK 005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): constipation (PT, AEs), stomatitis (PT, AEs), fever (PT, AEs), dizziness (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), fatigue (PT, severe AEs) and hyperglycaemia (PT, severe AEs).
c. No data available for the relevant subpopulation (see Section I 4.1 for reasons).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses of patient-reported outcomes on symptoms and health-related quality of life

Symptoms were recorded using the EORTC QLQ-C30 and FKSI-DRS. The FKSI-DRS (a subscale of the FKSI-15) is a validated questionnaire that is used to record disease-related symptoms in patients with advanced renal cell carcinoma [15]. The FKSI-DRS consists of 9 questions on specific symptoms, each with 5 possible answer options. In the FKSI-DRS total score, high values mean a low symptom burden and low values mean a high symptom burden.

In Module 4A, the company presented responder analyses for the time to first deterioration for the outcomes symptoms (EORTC QLQ-C30 and FKSI-DRS), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30) using the following response criteria:

- EORTC QLQ-C30: deterioration by ≥ 10 points each (respective scale range 0 to 100)
- FKSI-DRS: deterioration by ≥ 6 points (scale range 0 through 36)

- EQ-5D VAS: deterioration by ≥ 15 points (scale range 0 to 100)

The response criteria of the FKSI-DRS and the EQ-5D VAS were not pre-specified in the study protocol. Since the response criteria used for the analyses correspond to the criteria described in the General Methods of the Institute [16] for response criteria that reliably reflect a change that is noticeable to patients, the responder analyses are taken into account for the benefit assessment.

Analyses on the outcomes of the side effects category

Pneumonitis (PT, severe AEs)

The dossier provided no data for the relevant subpopulation for the outcome pneumonitis (PT, severe AEs). This is probably due to the low number of events that occurred (in Module 4A, the company presents analyses of severe AEs according to SOC and PT that occur in at least 5% of patients in one study arm or in at least 10 patients and at least 1% of patients in one study arm in accordance with the module template). In the total study population, only a few patients were affected by severe pneumonitis (1 patient in the intervention arm and 14 patients in the comparator arm).

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: belzutifan versus everolimus

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Hypoxia (PT, severe AEs[a])	Anaemia (PT, severe AEs)[a]	Pneumonitis (PT, severe AEs)[a]	Infections and infestations (SOC, severe AEs)[a]	Other specific AEs[b]
LITESPARK 005	L	L	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[d]	H[d]	H[f]	H[c, d]	H[d]	–[g]	H[d]	H[c, d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): constipation (PT, AEs), stomatitis (PT, AEs), fever (PT, AEs), dizziness (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), fatigue (PT, severe AEs) and hyperglycaemia (PT, severe AEs).
c. Lack of blinding in subjective recording of outcomes; applies to the other specific AEs for non-severe AEs.
d. Incomplete observations for potentially informative reasons.
e. Marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms.
f. Lack of blinding in the presence of subjective decision on treatment discontinuation.
g. No data available for the relevant subpopulation (see Section I 4.1 for reasons).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

There was a low risk of bias for the results of the outcome overall survival.

The results on morbidity and health-related quality of life, recorded using the EORTC QLQ-C30, FKSI-DRS and EQ-5D VAS instruments, have a high risk of bias. One reason for this is the lack of blinding, as the outcomes are recorded subjectively by the patients. Furthermore, the proportion of missing questionnaires increased sharply over the course of the study and differed between the treatment arms. These shortened observation periods are mainly due to potentially informative reasons, caused by the linking of the questionnaire recordings to the study treatment or disease progression (see Table 8).

The risk of bias for the results of the outcome discontinuation due to AEs was high because of the unblinded study design in the presence of subjective decision on treatment discontinuation. The certainty of results is additionally limited by the fact that treatment can

also be discontinued for reasons other than AEs. These reasons represent a competing event for the outcome cancellation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

For the other results in the side effects category, the high risk of bias was due to the shortened observations for potentially informative reasons. These result from the fact that the recording of side effects is linked to the end of the study treatment (see Table 8). In addition, the unblinded study design leads to a high risk of bias in the non-severe/non-serious side effects due to the subjective recording of outcomes.

Summary assessment of the certainty of conclusions

It is assumed that everolimus is a suitable individualized treatment option for the patients in the LITESPARK 005 study and that the ACT is sufficiently implemented for these patients in the present treatment situation (for a detailed explanation, see the text section on the implementation of the ACT in Section I 3.2 of the LITESPARK 005 study). However, it cannot be ruled out that another treatment option included in the G-BA's ACT would have been more suitable for some of the patients included. It therefore remains unclear whether the results of the study can be transferred to the German health care context without restriction. Based on the LITESPARK 005 study, at most hints, e.g. of an added benefit, can be derived for all outcomes irrespective of the outcome-specific risk of bias.

I 4.3 Results

Table 15 summarizes the results of the comparison of belzutifan with everolimus in adult patients with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

The Kaplan-Meier curves on the time-to-event analyses shown are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study outcome category outcome	Belzutifan N	Belzutifan median time to event in months [95% CI] patients with event n (%)	Everolimus N	Everolimus median time to event in months [95% CI] patients with event n (%)	Belzutifan vs. everolimus HR [95% CI]; p-value[a]
LITESPARK 005					
Mortality					
Overall survival	188	21.8 [17.4; 25.8] 128 (68.1)	182	18.1 [14.2; 23.9] 125 (68.7)	0.94 [0.74; 1.21]; 0.650
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration)[b]					
Fatigue	178	1.9 [1.1; 2.1] 126 (70.8)	164	1.9 [1.0; 2.0] 124 (75.6)	0.80 [0.62; 1.03]; 0.086
Nausea and vomiting	178	11.9 [6.4; 26.0] 80 (44.9)	164	10.0 [3.7; 15.4] 66 (40.2)	0.89 [0.64; 1.25]; 0.510
Pain	178	3.8 [2.1; 5.3] 105 (59.0)	164	2.8 [1.9; 3.0] 106 (64.6)	0.73 [0.55; 0.96]; 0.023
Dyspnoea	178	8.2 [3.7; 17.5] 87 (48.9)	164	3.7 [2.8; 7.9] 84 (51.2)	0.77 [0.57; 1.05]; 0.101
Insomnia	178	11.1 [5.5; 24.8] 81 (45.5)	164	3.7 [2.8; 5.6] 87 (53.0)	0.64 [0.47; 0.87]; 0.005
Appetite loss	178	17.4 [9.3; 27.6] 76 (42.7)	164	3.7 [2.8; 4.7] 88 (53.7)	0.51 [0.37; 0.70]; < 0.001
Constipation	178	15.7 [4.8; 24.9] 78 (43.8)	164	13.0 [9.0; 16.9] 59 (36.0)	1.14 [0.81; 1.61]; 0.443
Diarrhoea	178	21.6 [8.2; NC] 59 (33.1)	164	5.6 [3.7; 13.8] 73 (44.5)	0.53 [0.37; 0.75]; < 0.001
Symptoms (FKSI-DRS – time to first deterioration[c])	179	27.2 [17.7; NC] 62 (34.6)	165	10.1 [7.5; 16.7] 60 (36.4)	0.66 [0.46; 0.95]; 0.027
Health status (EQ-5D VAS, time to first deterioration[d])	179	9.3 [7.4; 20.3] 86 (48.0)	164	10.2 [5.5; 16.6] 67 (40.9)	0.90 [0.65; 1.25]; 0.528
Health-related quality of life					
EORTC-QLQ C30 – time to first deterioration[e]					
Global health status	178	4.6 [2.8; 5.6] 114 (64.0)	164	2.8 [1.9; 4.5] 99 (60.4)	0.77 [0.59; 1.02]; 0.071
Physical functioning	178	4.8 [2.8; 11.1] 100 (56.2)	164	3.1 [2.6; 4.9] 100 (61.0)	0.76 [0.57; 1.01]; 0.060

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study outcome category outcome	Belzutifan N	Belzutifan median time to event in months [95% CI] patients with event n (%)	Everolimus N	Everolimus median time to event in months [95% CI] patients with event n (%)	Belzutifan vs. everolimus HR [95% CI]; p-value[a]
Role functioning	178	2.8 [1.9; 4.6] 114 (64.0)	164	1.9 [1.7; 2.8] 110 (67.1)	0.80 [0.61; 1.04]; 0.097
Emotional functioning	178	6.4 [3.7; 15.7] 91 (51.1)	164	4.5 [2.8; 8.3] 80 (48.8)	0.86 [0.63; 1.17]; 0.330
Cognitive functioning	178	2.8 [1.9; 4.2] 121 (68.0)	164	3.7 [2.8; 5.5] 87 (53.0)	1.13 [0.86; 1.50]; 0.371
Social functioning	178	4.8 [2.8; 12.0] 97 (54.5)	164	2.8 [1.9; 4.6] 98 (59.8)	0.76 [0.57; 1.00]; 0.054
Side effects					
AEs (supplementary information)	186	0.4 [0.3; 0.5][f] 185 (99.5)	177	0.3 [0.3; 0.4][f] 175 (98.9)	–
SAEs	186	22.7 [13.5; NC][f] 83 (44.6)	177	15.9 [11.8; 28.2][f] 69 (39.0)	0.93 [0.67; 1.29]; 0.651
Severe AEs[g]	186	6.4 [3.7; 8.9][f] 123 (66.1)	177	4.6 [3.4; 6.7][f] 105 (59.3)	0.88 [0.67; 1.15]; 0.340
Discontinuation due to AEs	186	NA 13 (7.0)	177	31.4 [24.0; NC][f] 25 (14.1)	0.35 [0.17; 0.70]; 0.003
Hypoxia (PT, severe AEs)[g]	186	NA 26 (14.0)	177	NA 1 (0.6)	22.33 [3.02; 165.09]; 0.002
Anaemia (PT, severe AEs)[g]	186	27.5 [16.5; NC][f] 58 (31.2)	177	NA [15.7; NC][f] 30 (16.9)	1.41 [0.90; 2.21]; 0.133
Pneumonitis (PT, severe AEs)[g]	No suitable data				
Infections and infestations (SOC, severe AEs)[g]	186	NA 23 (12.4)	177	27.5 [14.4; NC][f] 37 (20.9)	0.38 [0.22; 0.66]; < 0.001
Other specific AEs					
Constipation (PT, AEs)	186	NA 32 (17.2)	177	NA 10 (5.6)	2.86 [1.40; 5.85]; 0.004
Stomatitis (PT, AEs)	186	NA 5 (2.7)	177	NA [13.4; NC][f] 65 (36.7)	0.05 [0.02; 0.13]; < 0.001
Pyrexia (PT, AEs)	186	NA 12 (6.5)	177	NA 22 (12.4)	0.38 [0.18; 0.78]; 0.008
Dizziness (PT, AEs)	186	NA [34.2; NC][f] 30 (16.1)	177	NA 2 (1.1)	11.41 [2.70; 48.16]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study outcome category outcome	Belzutifan		Everolimus		Belzutifan vs. everolimus
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Skin and subcutaneous tissue disorders (SOC, AEs)	186	NA [25.3; NC][f] 48 (25.8)	177	4.6 [1.7; NC][f] 89 (50.3)	0.36 [0.25; 0.51]; < 0.001
Fatigue (PT, severe AEs)[g]	186	NA 1 (0.5)	177	NA 10 (5.6)	0.07 [0.01; 0.53]; 0.010
Hyperglycaemia (PT, severe AEs)[g]	186	NA 3 (1.6)	177	NA 11 (6.2)	0.17 [0.04; 0.64]; 0.009

a. HR and CI: Cox proportional hazards model with treatment as covariate; 2-sided p-value: Wald test.
b. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. An FKSI-DRS score decrease by ≥ 6 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 36).
d. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. Institute's calculation: conversion from weeks to months.
g. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see also Section I 4.2).

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

No statistically significant difference between the treatment arms was shown for the scales fatigue, nausea and vomiting, dyspnoea and constipation. In each case, there was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

A statistically significant effect in favour of belzutifan in comparison with everolimus was shown for each of the scales insomnia, appetite loss and diarrhoea. In each case, this results in a hint of an added benefit of belzutifan in comparison with everolimus.

There is a statistically significant difference between the treatment arms for the pain scale, but the extent of the effect is no more than minor. However, there is an effect modification by the characteristic age (see Section I 4.4). There is a hint of an added benefit of belzutifan in comparison with everolimus for patients aged ≥ 65 years. For patients < 65 years, there is no hint of an added benefit of belzutifan compared to everolimus; an added benefit is therefore not proven.

FKSI-DRS

A statistically significant effect in favour of belzutifan in comparison with everolimus was shown for the outcome symptoms, recorded with the FKSI-DRS. However, the magnitude of the effect for these non-serious/non-severe symptoms (see Section I 5.1) is no more than minor. There was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome health status, recorded with the EQ-5D VAS. There was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning)

No statistically significant difference between the treatment arms was found for any of the scales global health status, role functioning, emotional functioning and cognitive functioning of the EORTC QLQ-C30. In each case, there was no hint of an added benefit of belzutifan in comparison with everolimus; an added benefit was therefore not proven.

There was no statistically significant difference between the treatment arms for the physical functioning scale. However, there is an effect modification for the characteristic IMDC risk category (see Section I 4.4). For patients with a poor IMDC risk category, there is a hint of an added benefit of belzutifan over everolimus. For patients with a favourable or intermediate IMDC risk category, there is no hint of an added benefit of belzutifan over everolimus; an added benefit is therefore not proven for this patient group.

No statistically significant difference between the treatment arms was found for the social functioning scale. However, there is an effect modification by the characteristic age (see Section I 4.4). For patients ≥ 65 years, there is a hint of an added benefit of belzutifan over everolimus. For patients < 65 years, there is no hint of an added benefit of belzutifan over everolimus; an added benefit is therefore not proven for this patient group.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

There is no statistically significant difference between the treatment arms for the outcome severe AEs. There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference in favour of belzutifan compared with everolimus was shown for the outcome discontinuation due to AEs. However, there is an effect modification by the characteristic age (see Section I 4.4). There is a hint of lesser harm from belzutifan in comparison with everolimus for patients aged ≥ 65 years. For patients < 65 years, there was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Specific AEs

Hypoxia (PT, severe AEs)

For the outcome hypoxia (PT, severe AEs), a statistically significant difference was found to the disadvantage of belzutifan in comparison with everolimus. There is a hint of greater harm from belzutifan in comparison with everolimus.

Anaemia (PT, severe AEs)

No statistically significant difference between the treatment arms was found for the outcome anaemia (PT, severe AEs). There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Pneumonitis (PT, severe AEs)

No suitable data are available for the outcome pneumonitis (PT, severe AEs). There was no hint of greater or lesser harm from belzutifan in comparison with everolimus; greater or lesser harm is therefore not proven.

Infections and infestations (SOC, severe AEs)

A statistically significant difference in favour of belzutifan compared with everolimus was shown for the outcome infections and infestations (SOC, severe AEs). There is a hint of lesser harm from belzutifan in comparison with everolimus.

Further specific AEs - constipation (PT, AEs), stomatitis (PT, AEs), fever (PT, AEs), dizziness (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), fatigue (PT, severe AEs) and hyperglycaemia (PT, severe AEs)

For each of the outcomes stomatitis (PT, AEs), fever (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), fatigue (PT, severe AEs) and hyperglycaemia (PT, severe AEs), there was a statistically significant difference in favour of belzutifan compared to everolimus. In each case, there is a hint of lesser harm from belzutifan in comparison with everolimus.

For each of the outcomes constipation (PT, AEs) and dizziness (PT, AEs), a statistically significant difference was found to the disadvantage of belzutifan in comparison with everolimus. There is a hint of greater harm from belzutifan in comparison with everolimus in each case.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- IMDC risk category (favourable vs. intermediate vs. poor)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup

results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 16. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B of the full dossier assessment.

Table 16: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study outcome characteristic subgroup	Belzutifan		Everolimus		Belzutifan vs. everolimus	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
LITESPARK 005						
Symptoms (EORTC QLQ-C30, pain – time to first deterioration[c])						
Age						
< 65 years	113	3.8 [1.9; 5.3] 69 (61.1)	89	3.7 [2.8; 7.3] 51 (57.3)	1.04 [0.72; 1.49]	0.849
≥ 65 years	65	2.8 [1.9; 20.3] 36 (55.4)	75	1.9 [1.0; 1.9] 55 (73.3)	0.41 [0.26; 0.63]	< 0.001
					Interaction:	0.001[c]
Health-related quality of life (EORTC QLQ-C30, physical functioning - time to first deterioration[d]						
IMDC risk category						
Favourable	41	11.1 [2.8; 20.3] 22 (53.7)	39	2.8 [1.9; 16.6] 21 (53.8)	0.71 [0.39; 1.31]	0.276
Intermediate	115	2.8 [1.9; 7.4] 73 (63.5)	106	3.5 [2.1; 5.5] 66 (62.3)	0.92 [0.66; 1.30]	0.640
Poor	22	NA [3,7; NC] 5 (22,7)	19	3.1 [1.0; 12.5] 13 (68.4)	0.22 [0.07; 0.62]	0.004
					Interaction:	0.036[c]
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[d]						
Age						
< 65 years	113	2.9 [1.9; 8.4] 62 (54.9)	89	2.8 [1.9; 12.5] 50 (56.2)	0.98 [0.67; 1.43]	0.923
≥ 65 years	65	8.3 [2.8; 16.9] 35 (53.8)	75	2.7 [1.8; 3.9] 48 (64.0)	0.46 [0.29; 0.73]	0.001
					Interaction:	0.050[c,e]

Table 16: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: belzutifan versus everolimus (multipage table)

Study outcome characteristic subgroup	Belzutifan N	Belzutifan median time to event in months [95 % CI] patients with event n (%)	Everolimus N	Everolimus median time to event in months [95 % CI] patients with event n (%)	Belzutifan vs. everolimus HR [95% CI][a]	Belzutifan vs. everolimus p-value[a]
Discontinuation due to AEs						
Age						
< 65 years	120	NA 9 (7.5)	97	31.4 [NC][f] 7 (7.2)	0.66 [0.23; 1.87]	0.435
≥ 65 years	66	NA 4 (6.1)	80	NA [24.0; NC][f] 18 (22.5)	0.21 [0.07; 0.63]	0.005
					Interaction:	0.033[c]

a. HR and CI: Cox proportional hazards model with treatment as covariate; 2-sided p-value (Wald test).
b. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. Cox proportional hazards model with treatment and subgroup as covariates and interaction between treatment and subgroup (p-value based on likelihood ratio test).
d. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. Unrounded p-value of the interaction < 0.05.
f. Institute's calculation.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial

Morbidity

Symptoms (EORTC QLQ-C30)

Pain

An effect modification by the characteristic age was found for the pain scale of the EORTC QLQ-C30..

A statistically significant difference in favour of belzutifan was shown for the age group ≥ 65 years of age. There was a hint of added benefit of belzutifan in comparison with everolimus for this patient group.

There was no statistically significant difference between the treatment arms for patients < 65 years. There was no hint of added benefit of belzutifan in comparison with everolimus for this patient group; an added benefit is therefore not proven.

Health-related quality of life (EORTC QLQ-C30)

Physical functioning

An effect modification for the characteristic IMDC risk category was found for the physical functioning scale of the EORTC QLQ-C30.

For patients with a poor IMDC risk category, there is a statistically significant difference in favour of belzutifan over everolimus. There was a hint of added benefit of belzutifan in comparison with everolimus for this patient group.

For patients with favourable or intermediate IMDC risk categories, there was no statistically significant difference between the treatment arms. In each case, there was no hint of added benefit of belzutifan in comparison with everolimus for this patient groups; an added benefit is therefore not proven.

Social functioning

An effect modification for the characteristic age was found for the social functioning scale of the EORTC QLQ-C30..

A statistically significant difference in favour of belzutifan compared to everolimus was shown for the age group ≥ 65 years. There was a hint of added benefit of belzutifan in comparison with everolimus for this patient group.

There was no statistically significant difference between the treatment arms for patients < 65 years. There was no hint of added benefit of belzutifan in comparison with everolimus for this patient group; an added benefit is therefore not proven.

Side effects

Discontinuation due to AEs

There was an effect modification for the characteristic age for the outcome of discontinuation due to AEs.

A statistically significant difference in favour of belzutifan compared to everolimus was shown for the age group ≥ 65 years. There was a hint of lesser harm from belzutifan in comparison with everolimus for this patient group.

There was no statistically significant difference between the treatment arms for patients < 65 years. There was no hint of greater or lesser harm from belzutifan in comparison with everolimus for this patient group; greater or lesser harm is therefore not proven.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [16].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier does not provide any details as to whether the outcomes on symptoms and on side effects were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

EORTC QLQ-C30 (pain, insomnia, appetite loss and diarrhoea) and FKSI-DRS

For the scales of pain, insomnia, appetite loss and diarrhoea of the EORTC QLQ-C30 as well as for the outcome symptoms, recorded using FKSI-DRS, there is insufficient information available to classify the severity category as serious/severe. These outcomes are therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, the dossier provides no information on the severity of the events that occurred, neither for the relevant subpopulation nor for the subgroup analyses on the characteristic age. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: belzutifan vs. everolimus (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Belzutifan vs. everolimus** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	21.8 vs. 18.1 months HR: 0.94 [0.74; 1.21]; p = 0.650	Lesser benefit/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	1.9 vs. 1.9 months HR: 0.80 [0.62; 1.03]; p = 0.086	Lesser benefit/added benefit not proven
Nausea and vomiting	11.9 vs. 10.0 months HR: 0.89 [0.64; 1.25]; p = 0.510	Lesser benefit/added benefit not proven
Pain		
Age		
< 65 years	3.8 vs. 3.7 months HR: 1.04 [0.72; 1.49]; p = 0.849	Lesser benefit/added benefit not proven
≥ 65 years	2.8 vs. 1.9 months HR: 0.41 [0.26; 0.63] p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: considerable
Dyspnoea	8.2 vs. 3.7 months HR: 0.77 [0.57; 1.05]; p = 0.101	Lesser benefit/added benefit not proven
Insomnia	11.1 vs. 3.7 months HR: 0.64 [0.47; 0.87]; p = 0.005 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications 0.80 ≤ CI_u < 0.90 added benefit, extent: minor
Appetite loss	17.4 vs. 3.7 months HR: 0.51 [0.37; 0.70]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: considerable
Constipation	15.7 vs. 13.0 months HR: 1.14 [0.81; 1.61]; p = 0.443	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: belzutifan vs. everolimus (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Belzutifan vs. everolimus** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Diarrhoea	21.6 vs. 5.6 months HR: 0.53 [0.37; 0.75]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: considerable
Symptoms (FKSI-DRS – time to first deterioration)	27.2 vs. 10.1 months HR: 0.66 [0.46; 0.95]; p = 0.027	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 lesser benefit/added benefit not proven[c]
Health status (EQ-5D VAS, time to first deterioration)	9.3 vs. 10.2 months HR: 0.90 [0.65; 1.25]; p = 0.528	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	4.6 vs. 2.8 months HR: 0.77 [0.59; 1.02]; p = 0.071	Lesser benefit/added benefit not proven
Physical functioning		
IMDC		
Favourable	11.1 vs. 2.8 months HR: 0.71 [0.39; 1.31]; p = 0.276	Lesser benefit/added benefit not proven
Intermediate	2.8 vs. 3.5 months HR: 0.92 [0.66; 1.30]; p = 0.640	Lesser benefit/added benefit not proven
Poor	NA vs. 3.1 months HR: 0.22 [0.07; 0.62]; p = 0.004 probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Role functioning	2.8 vs. 1.9 months HR: 0.80 [0.61; 1.04]; p = 0.097	Lesser benefit/added benefit not proven
Emotional functioning	6.4 vs. 4.5 months HR: 0.86 [0.63; 1.17]; p = 0.330	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: belzutifan vs. everolimus (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Belzutifan vs. everolimus** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Cognitive functioning	2.8 vs. 3.7 months HR: 1.13 [0.86; 1.50]; p = 0.371	Lesser benefit/added benefit not proven
Social functioning		
Age		
< 65 years	2.9 vs. 2.8 months HR: 0.98 [0.67; 1.43]; p = 0.923	Lesser benefit/added benefit not proven
≥ 65 years	8.3 vs. 2.7 months HR: 0.46 [0.29; 0.73]; p = 0.001 probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Side effects		
SAE	22.7 vs. 15.9 months HR: 0.93 [0.67; 1.29]; p = 0.651	Greater/lesser harm not proven
Severe AEs	6.4 vs. 4.6 months HR: 0.88 [0.67; 1.15]; p = 0.340	Greater/lesser harm not proven
Discontinuation due to AEs		
Age		
< 65 years	NA vs. 31.4 months HR: 0.66 [0.23; 1.87]; p = 0.435	Greater/lesser harm not proven
≥ 65 years	NA vs. NA HR: 0.21 [0.07; 0.63]; p = 0.005 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser harm, extent: “considerable”
Hypoxia (severe AEs)	NA vs. NA HR: 22.33 [3.02; 165.09]; HR: 0.04 [0.01; 0.33][d]; p = 0.002 probability: hint	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Anaemia (severe AEs)	27.5 months vs. NA HR: 1.41 [0.90; 2.21]; p = 0.133	Greater/lesser harm not proven
Pneumonitis (severe AEs)	No suitable data	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: belzutifan vs. everolimus (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Belzutifan vs. everolimus** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infections and infestations (severe AEs)	NA vs. 27.5 months HR: 0.38 [0.22; 0.66]; p < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% lesser harm, extent: “major”
Constipation (AEs)	NA vs. NA HR: 2.86 [1.40; 5.85]; HR: 0.35 [0.17; 0.71][d]; p = 0.004 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 greater harm, extent: “considerable”
Stomatitis (AEs)	NA vs. NA HR: 0.05 [0.02; 0.13]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser harm, extent: “considerable”
Pyrexia (AEs)	NA vs. NA HR: 0.38 [0.18; 0.78]; p = 0.008 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser harm, extent: “considerable”
Dizziness (AEs)	NA vs. NA HR: 11.41 [2.70; 48.16]; HR: 0.09 [0.02; 0.37][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 greater harm, extent: “considerable”
Skin and subcutaneous tissue disorders (AEs)	NA vs. 4.6 months HR: 0.36 [0.25; 0.51]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser harm, extent: “considerable”
Fatigue (severe AEs)	NA vs. NA HR: 0.07 [0.01; 0.53]; p = 0.010 probability: hint	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% lesser harm, extent: “major”
Hyperglycaemia (severe AEs)	NA vs. NA HR: 0.17 [0.04; 0.64]; p = 0.009 probability: hint	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% lesser harm, extent: “major”

Table 17: Extent of added benefit at outcome level: belzutifan vs. everolimus (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Belzutifan vs. everolimus** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms; HR: Hazard Ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of belzutifan in comparison with everolimus

Positive effects	**Negative effects**
Outcomes with shortened observation period	
Morbidity ▪ symptoms (EORTC QLQ-C30) ▫ pain - age (≥ 65 years): hint of added benefit – extent: “considerable” ▫ insomnia: hint of an added benefit – extent: “minor” ▫ appetite loss: hint of an added benefit – extent: considerable ▫ diarrhoea: hint of an added benefit – extent: “considerable”	–
Health-related quality of life (EORTC QLQ-C30) ▪ physical functioning: ▫ IMDC (poor): hint of added benefit – extent: "major" ▪ social functioning ▫ age (≥ 65 years): hint of added benefit – extent: "major"	–
Serious/severe side effects ▪ infections and infestations (severe AEs), fatigue (severe AEs), hyperglycaemia (severe AEs): in each case proof of lesser harm - extent: “major”	Serious/severe side effects ▪ hypoxia (severe AEs): hint of greater harm – extent: “major”
Non-serious/non-severe side effects ▪ discontinuation due to AEs ▫ age (≥ 65 years): hint of lesser harm – extent: "considerable" ▪ stomatitis (AEs), fever (AEs), skin and subcutaneous tissue disorders (AEs): in each case hint of lesser harm – extent: “considerable”	Non-serious/non-severe side effects ▪ constipation (AEs), dizziness (AEs): in each case hint of greater harm – extent: “considerable”
There are no suitable data on the outcome pneumonitis (PT, severe AEs).	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event	

In this benefit assessment, based on the LITESPARK 005 study, conclusions can only be drawn on those patients for whom everolimus is a suitable individualized comparator therapy (see Section I 3.2). Data for patients for whom everolimus is not a suitable individualized treatment are lacking.

Patients for whom everolimus is a suitable individualized treatment

Overall, both positive and negative effects of belzutifan were found in comparison with the ACT. The characteristics age and IMDC risk category are effect modifiers for several outcomes. Due to the effect modification by the characteristic age both for individual outcomes of symptoms and health-related quality of life (EORTC QLQ-C30) and for the outcome discontinuation due to AEs, the results on the added benefit of belzutifan compared with the ACT are derived separately for age groups below:

Patients aged ≥ 65 years

On the positive effects side, there are hints of an added benefit, in most cases with considerable extent, for several symptom scales recorded using the EORTC QLQ-C30. There are further positive effects in the side effects category for several specific AEs of different severity categories, each with considerable or major extent.

For patients ≥ 65 years, there are also hints of a considerable added benefit for the pain scale of the EORTC QLQ-C30 and for the outcome discontinuation due to AEs. In addition, there is a hint of major added benefit for this patient group in health-related quality of life for one scale (social functioning of the EORTC QLQ-C30).

On the other hand, there are negative effects for specific AEs in the side effects category of varying severity categories and with varying, partly major extent. Overall, these negative effects are not assumed to completely call into question the partially major effects in patients ≥ 65 years.

In summary, for adult patients ≥ 65 years of age with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies, and for whom everolimus is a suitable individualized treatment, there is a hint of considerable added benefit of belzutifan compared with the ACT.

Patients < 65 years

Analogous to patients ≥ 65, various positive effects were also shown for patients aged < 65 years for several symptom outcome scales (EORTC QLQ-C30) and for some specific AEs of different severity categories. For patients < 65 years, however, there were no effects on health-related quality of life or discontinuation due to AEs. On the other hand, there are negative effects for specific AEs of varying severity categories, some of them with major extent.

In summary, for adult patients < 65 years of age with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies, and for whom everolimus is a suitable individualized treatment, there is a hint of minor added benefit of belzutifan compared with the ACT.

Patients for whom everolimus is no suitable individualized treatment

For adult patients with advanced clear cell renal cell carcinoma whose disease has progressed after 2 or more therapies, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies, and for whom everolimus is not a suitable individualized treatment, there are no data for the assessment of the added benefit of belzutifan over the ACT from LITESPARK 005. An added benefit is therefore not proven for this patient group.

Table 19 shows a summary of probability and extent of the added benefit of belzutifan.

Table 19: Belzutifan – probability and extent of added benefit

Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adults with advanced clear cell renal cell carcinoma that has progressed following 2 or more therapies that included a PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies	Individualized treatment[c, d, e] choosing from ▪ axitinib, ▪ cabozantinib, ▪ everolimus, ▪ lenvatinib in combination with everolimus and ▪ sunitinib	▪ Patients for whom everolimus is a suitable individualized treatment[f]: ▫ < 65 years: hint of minor added benefit ▫ ≥ 65 years: hint of considerable added benefit ▪ patients for whom everolimus is not a suitable individualized treatment: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the treatment decision and that treatment is palliative.
c. The treatment decision is made under particular consideration of the prior therapy. When choosing the treatment option, a change of the tyrosinkinase inhibitor (TKI) must be made with regard to the previously administered TKI.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria.
e. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
f. The LITESPARK 005 study included only patients with a Karnofsky performance status ≥ 70 %. It remains unclear whether the observed effects can be transferred to patients with a Karnofsky performance status < 70 %.

ACT: appropriate comparator therapy G-BA: Federal Joint Committee; PD-(L)1: Programmed Cell Death Protein-(Ligand) 1; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

The assessment described above deviates from that of the company, which derives an indication of a considerable added benefit for all patients in this therapeutic indication, irrespective of age and the suitability of everolimus as an individualized treatment.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. 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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