# Relugolix (prostate cancer) –

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

**EXTRACT**

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[1] Translation of Sections I 1 to I 7 of the dossier assessment *Relugolix (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**Patient and family involvement**

The questionnaire on the disease and its treatment was answered by Udo Ehrmann.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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# Part I: Benefit assessment

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

# I List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| ADT | androgen deprivation therapy |
| AE | adverse event |
| CNS | central nervous system |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EPAR | European Public Assessment Report |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| GnRH | gonadotropin-releasing hormone |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MACE | major adverse cardiovascular event |
| MID | minimally important difference |
| PSA | prostate-specific antigen |
| PT | Preferred Term |
| QLQ-C30 | Quality of Life Questionnaire-Core 30 |
| QLQ-PR25 | Quality of Life Questionnaire-Prostate 25 |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SMQ | Standardized Medical Dictionary for Regulatory Activities Query |
| SPC | Summary of Product Characteristics |
| VAS | visual analogue scale |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug relugolix. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 October 2022.

### Research question

The aim of the present report is to assess the added benefit of relugolix in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced hormone-sensitive prostate cancer.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of relugolix (multipage table)

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| Patients with advanced hormone-sensitive prostate cancer[b] | | |
| 1 | Patients who are candidates for local therapy | ▪ radical prostatectomy, if necessary in combination with lymphadenectomy<br>or<br>▪ percutaneous radiotherapy in combination with conventional androgen deprivationc or bicalutamide<br>or<br>▪ percutaneous radiotherapy in combination with HDR brachytherapy (only for patients in clinical category cT3) |
| 2 | Patients who are not candidates for local therapy | ▪ conventional androgen deprivation[c]<br>or<br>▪ bicalutamide |
| 3 | Patients with PSA recurrence or clinical recurrence after primary local therapy | Individualized treatment[d] selected from<br>▪ salvage prostatectomy,<br>▪ percutaneous salvage radiotherapy, and<br>▪ percutaneous salvage radiotherapy in combination with conventional androgen deprivationc or bicalutamide;<br>taking into account the prior therapy and the risk of progression |

Table 2: Research questions of the benefit assessment of relugolix (multipage table)

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| Patients with metastatic hormone-sensitive prostate cancer (mHSPC)[e, f] | | |
| 4a | Patients who are candidates for combination therapy | ▪ conventional androgen deprivation[c] in combination with apalutamide<br>or<br>▪ conventional androgen deprivation[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer)<br>or<br>▪ conventional androgen deprivation[c] in combination with docetaxel with or without prednisone or prednisolone<br>or<br>▪ conventional androgen deprivation[c] in combination with enzalutamide |
| 4b | Patients who are not candidates for combination therapy | ▪ conventional androgen deprivation[c] |

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that there is no distant metastasis (M0). According to the G-BA, it is assumed that, when determining the ACT, the individual therapeutic decision in the target population was made against long-term observation. Watchful waiting is therefore not considered to be an ACT in the present case.
c. According to the G-BA, conventional androgen deprivation in the context of the present therapeutic indication means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. The drugs buserelin, leuprorelin, goserelin, triptorelin (GnRH agonists) and degarelix (GnRH antagonist) are considered suitable for the implementation of medical castration in the context of conventional androgen deprivation. In the context of a clinical study, the selection of only one of these drugs (single-comparator study) is considered sufficient.
d. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multi-comparator study).
e. It is assumed that there is distant metastasis (M1).
f. According to the G-BA, corresponding to the generally recognized state of medical knowledge, conventional androgen deprivation alone is only indicated for patients with mHSPC for whom a combination therapy – additional therapy to conventional androgen deprivation – is not an option with regard to any comorbidities and the general condition (research question 4b).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HDR: high dose rate; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen

The company followed the specification of the ACT.

In this benefit assessment, the subpopulations a to c and d1, d2 named by the G-BA and the company are referred to as research questions 1 to 3 and 4a, 4b, in accordance with the research questions in Table 2.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Below, research question 2 of the present benefit assessment is addressed first, as the company submitted data for the assessment of the added benefit of relugolix only for this research question. Subsequently, research questions 1 and 3 as well as research questions 4a and 4b are addressed together.

**Research question 2: patients who are not candidates for local therapy**

***Study pool and study design***

A subpopulation of the HERO study was used for the benefit assessment. The HERO study is an open-label RCT comparing relugolix with leuprorelin in patients with advanced hormone-sensitive prostate cancer. Patients had to be candidates for, in the opinion of the investigator, at least 1 year of androgen deprivation therapy (ADT) for the treatment of advanced hormone-sensitive prostate cancer. Patients whose disease fulfilled one of the following criteria were included:

- evidence of biochemical (prostate-specific antigen [PSA]) or clinical relapse following local primary intervention with curative intent, and not a candidate for salvage treatment by surgery (hereafter referred to as "Group A"), or
- newly diagnosed metastatic disease (hereafter referred to as "Group B"), or
- advanced localized disease that is unlikely to be cured with local primary intervention (surgery or radiation) with curative intent (hereafter referred to as "Group C").

Patients were not allowed to have a history of surgical castration. Also, patients were not allowed to have previously been treated with a gonadotropin-releasing hormone (GnRH) analogue or another form of ADT (oestrogen or anti-androgen) for more than 18 months. If the treatment duration was ≤ 18 months, then that therapy must have been completed at least 3 months prior to baseline. Enrolment was limited to patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

A total of 1078 patients were randomly allocated in a 2:1 ratio to treatment with relugolix (N = 719) or leuprorelin (N = 359). Randomization was stratified by region (North and South America/Europe/Asia and other regions), the presence of metastatic prostate cancer (yes/no) and age at baseline (≤ 75/> 75 years).

Treatment with relugolix was given as a daily oral dose (360 mg on day 1, 120 mg from day 2 onwards) in compliance with the Summary of Product Characteristics (SPC). Leuprorelin was administered as subcutaneous depot injection every 12 weeks. Treatment with 11.25 mg

leuprorelin in Japan, Taiwan and China, and with 22.5 mg leuprorelin in the other countries, was in compliance with the respective SPCs. In the leuprorelin arm, an antiandrogen could be administered for the first 4 weeks or longer if indicated, as determined by the investigator, which is largely in compliance with the SPC.

Treatment was given in both study arms for a maximum of 48 weeks or until unacceptable toxicity, dose interruption of relugolix > 10 days, or withdrawal of consent. Supplementary radiotherapy, cryotherapy or high frequency ultrasound was allowed no sooner than 2 months after initiation of treatment. However, palliative radiation to sites other than the prostate was permitted at earlier time points.

The primary outcome of the study was sustained testosterone suppression at castrate level. Patient-relevant secondary outcomes were overall survival, outcomes on morbidity, health-related quality of life, and adverse events (AEs).

*Relevant subpopulation*

The subpopulation of patients without distant metastasis is used for research question 2 of the present benefit assessment. There is uncertainty as to whether local therapy would no longer have been an option for all patients in this subpopulation according to research question 2. The uncertainty is taken into account in the certainty of conclusions.

*Data cut-offs*

The results used were from the final analysis with database lock on 23 September 2020.

***Risk of bias***

The risk of bias across outcomes is rated as low for the HERO study.

The risk of bias of the results for the outcomes of overall survival, serious AEs (SAEs) and severe AEs is rated as low.

The risk of bias of the results of the symptom and health-related quality of life outcomes recorded using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) is not assessed because the company did not present the required analyses with a response criterion of ≥ 10 points.

The risk of bias of the results for the outcome of health status, recorded with the EQ-5D visual analogue scale (VAS), is rated as high due to the lack of blinding in subjective recording of outcomes and due to the unclear proportion of patients included in the analysis.

The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding with subjective decision on discontinuation.

***Results***

*Mortality*

*Overall survival*

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

*Morbidity*

*Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25)*

The required analyses with a response criterion of ≥ 10 points are not available for the symptom outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. In each case, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

*Health status (EQ-5D visual analogue scale [VAS])*

Health status was surveyed by EQ-5D VAS. The time to deterioration by ≥ 15 points was used.

No statistically significant differences between treatment groups were found for the outcome of health status. There is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

*Health-related quality of life*

*EORTC QLQ-C30 and EORTC QLQ-PR25*

The required analyses with a response criterion of ≥ 10 points are not available for the health-related quality of life outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. In each case, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

*Side effects*

*SAEs, severe AEs, discontinuation due to AEs*

There were no statistically significant differences between treatment groups for the outcomes of SAEs, severe AEs and discontinuation due to AEs. There is no hint of greater or lesser harm from relugolix in comparison with leuprorelin for any of them; greater or lesser harm is therefore not proven.

*Specific AEs*

No specific AEs were selected.

### Research questions 1 and 3: patients who are candidates for local therapy, and patients with PSA recurrence or clinical recurrence after primary local therapy

#### *Results*

The company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with advanced hormone-sensitive prostate cancer who are candidates for local therapy (research question 1), and patients with PSA recurrence or clinical recurrence after primary local therapy (research question 3).

#### *Results on added benefit*

No data are available for the assessment of the added benefit of relugolix in comparison with the ACT in patients with advanced hormone-sensitive prostate cancer who are candidates for local therapy (research question 1), and patients with PSA recurrence or clinical recurrence after primary local therapy (research question 3). This results in no hint of added benefit of relugolix in comparison with the ACT for research question 1 or research question 3; an added benefit is therefore not proven.

### Research questions 4a and 4b: patients with mHSPC who are candidates for combination therapy or who are not candidates for combination therapy

#### *Results*

The company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with mHSPC who are candidates for combination therapy (research question 4a) or who are not candidates for combination therapy (research question 4b).

#### *Results on added benefit*

No data are available for the assessment of the added benefit of relugolix in comparison with the ACT in patients with mHSPC who are candidates for combination therapy (research question 4a) or who are not candidates for combination therapy (research question 4b). For patients with mHSPC, this results in no hint of added benefit of relugolix in comparison with the ACT for research question 4a or research question 4b of the present benefit assessment; an added benefit is therefore not proven.

**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 relugolix in comparison with the ACT are assessed as follows:

***Research question 2: patients who are not candidates for local therapy***

Overall, neither positive nor negative effects were found. The company did not provide the required analyses with a response criterion of ≥ 10 points for the symptom and health-related quality of life outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. When looking at the results with a response criterion of ≥ 15 points, there is no statistically significant difference between the treatment groups in any scale, except for a no more than marginal effect in the diarrhoea scale of the EORTC QLQ-C30. For the EORTC QLQ-PR25 scale on micturition problems, there may be a negative effect if the response criterion of ≥ 10 points is applied.

In summary, there is no added benefit of relugolix in comparison with the ACT for patients with advanced hormone-sensitive prostate cancer who are not candidates for local therapy.

***Research questions 1 and 3: patients who are candidates for local therapy, and patients with PSA recurrence or clinical recurrence after primary local therapy***

The company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with advanced hormone-sensitive prostate cancer who are candidates for local therapy (research question 1), and patients with PSA recurrence or clinical recurrence after primary local therapy (research question 3). An added benefit for these patients is not proven.

***Research questions 4a and 4b: patients with mHSPC who are candidates for combination therapy or who are not candidates for combination therapy***

The company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with mHSPC who are candidates for combination therapy (research question 4a) or who are not candidates for combination therapy (research question 4b). An added benefit for these patients is not proven.

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

Table 3 summarizes the probability and extent of added benefit of relugolix.

Table 3: Relugolix – probability and extent of added benefit (multipage table)

| **Research question** | **Therapeutic indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|---|
| Patients with advanced hormone-sensitive prostate cancer[b] | | | |
| 1 | Patients who are candidates for local therapy | ▪ radical prostatectomy, if necessary in combination with lymphadenectomy<br>or<br>▪ percutaneous radiotherapy in combination with conventional androgen deprivation[c] or bicalutamide<br>or<br>▪ percutaneous radiotherapy in combination with HDR brachytherapy (only for patients in clinical category cT3) | Added benefit not proven |
| 2 | Patients who are not candidates for local therapy | ▪ conventional androgen deprivation[c]<br>or<br>▪ bicalutamide | Added benefit not proven[d] |
| 3 | Patients with PSA recurrence or clinical recurrence after primary local therapy | Individualized treatment[e] selected from<br>▪ salvage prostatectomy,<br>▪ percutaneous salvage radiotherapy, and<br>▪ percutaneous salvage radiotherapy in combination with conventional androgen deprivationc or bicalutamide;<br>taking into account the prior therapy and the risk of progression | Added benefit not proven |
| Patients with metastatic hormone-sensitive prostate cancer (mHSPC)[f, g] | | | |
| 4a | Patients who are candidates for combination therapy | ▪ conventional androgen deprivation[c] in combination with apalutamide<br>or<br>▪ conventional androgen deprivation[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer)<br>or<br>▪ conventional androgen deprivation[c] in combination with docetaxel with or without prednisone or prednisolone<br>or<br>▪ conventional androgen deprivation[c] in combination with enzalutamide | Added benefit not proven |

Table 3: Relugolix – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| 4b | Patients who are not candidates for combination therapy | ▪ conventional androgen deprivation[c] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that there is no distant metastasis (M0). According to the G-BA, it is assumed that, when determining the ACT, the individual therapeutic decision in the target population was made against long-term observation. Watchful waiting is therefore not considered to be an ACT in the present case.
c. According to the G-BA, conventional androgen deprivation in the context of the present therapeutic indication means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. The drugs buserelin, leuprorelin, goserelin, triptorelin (GnRH agonists) and degarelix (GnRH antagonist) are considered suitable for the implementation of medical castration in the context of conventional androgen deprivation. In the context of a clinical study, the selection of only one of these drugs (single-comparator study) is considered sufficient.
d. The HERO study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
e. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multi-comparator study).
f. It is assumed that there is distant metastasis (M1).
g. According to the G-BA, corresponding to the generally recognized state of medical knowledge, conventional androgen deprivation alone is only indicated for patients with mHSPC for whom a combination therapy – additional therapy to conventional androgen deprivation – is not an option with regard to any comorbidities and the general condition (research question 4b).

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HDR: high dose rate; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen

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 the present report is to assess the added benefit of relugolix in comparison with the ACT in adult patients with advanced hormone-sensitive prostate cancer.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of relugolix (multipage table)

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| Patients with advanced hormone-sensitive prostate cancer[b] | | |
| 1 | Patients who are candidates for local therapy | ▪ radical prostatectomy, if necessary in combination with lymphadenectomy<br>or<br>▪ percutaneous radiotherapy in combination with conventional androgen deprivation[c] or bicalutamide<br>or<br>▪ percutaneous radiotherapy in combination with HDR brachytherapy (only for patients in clinical category cT3) |
| 2 | Patients who are not candidates for local therapy | ▪ conventional androgen deprivation[c]<br>or<br>▪ bicalutamide |
| 3 | Patients with PSA recurrence or clinical recurrence after primary local therapy | Individualized treatment[d] selected from<br>▪ salvage prostatectomy,<br>▪ percutaneous salvage radiotherapy, and<br>▪ percutaneous salvage radiotherapy in combination with conventional androgen deprivationc or bicalutamide;<br>taking into account the prior therapy and the risk of progression |
| Patients with metastatic hormone-sensitive prostate cancer (mHSPC)[e, f] | | |
| 4a | Patients who are candidates for combination therapy | ▪ conventional androgen deprivation[c] in combination with apalutamide<br>or<br>▪ conventional androgen deprivation[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer)<br>or<br>▪ conventional androgen deprivation[c] in combination with docetaxel with or without prednisone or prednisolone<br>or<br>▪ conventional androgen deprivation[c] in combination with enzalutamide |
| 4b | Patients who are not candidates for combination therapy | ▪ conventional androgen deprivation[c] |

Table 4: Research questions of the benefit assessment of relugolix (multipage table)

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| a. Presented is the respective ACT specified by the G-BA.<br>b. It is assumed that there is no distant metastasis (M0). According to the G-BA, it is assumed that, when determining the ACT, the individual therapeutic decision in the target population was made against long-term observation. Watchful waiting is therefore not considered to be an ACT in the present case.<br>c. According to the G-BA, conventional androgen deprivation in the context of the present therapeutic indication means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. The drugs buserelin, leuprorelin, goserelin, triptorelin (GnRH agonists) and degarelix (GnRH antagonist) are considered suitable for the implementation of medical castration in the context of conventional androgen deprivation. In the context of a clinical study, the selection of only one of these drugs (single-comparator study) is considered sufficient.<br>d. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multi-comparator study).<br>e. It is assumed that there is distant metastasis (M1).<br>f. According to the G-BA, corresponding to the generally recognized state of medical knowledge, conventional androgen deprivation alone is only indicated for patients with mHSPC for whom a combination therapy – additional therapy to conventional androgen deprivation – is not an option with regard to any comorbidities and the general condition (research question 4b).<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HDR: high dose rate; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen | | |

The company followed the specification of the ACT. However, the company noted that relugolix is only indicated in patients with advanced hormone-sensitive prostate cancer who require ADT as the sole therapy or as part of a combination. For these patients, relugolix could replace the respective conventional ADT, but not a combined treatment with e.g. radiotherapy, hormone therapy or chemotherapy, according to the company. In the opinion of the company, a comparison of relugolix with ADT in combination with radiotherapy, hormone therapy or chemotherapy is therefore not appropriate. Since the company nevertheless followed the ACT, the objections of the company regarding the ACT are of no consequence for the present benefit assessment.

In this benefit assessment, the subpopulations a to c and d1, d2 named by the G-BA and the company are referred to as research questions 1 to 3 and 4a, 4b, in accordance with the research questions in Table 4.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

In the following Chapter I 3, research question 2 of the present benefit assessment is addressed first, as the company submitted data for the assessment of the added benefit of

relugolix only for this research question. Subsequently, research questions 1 and 3 (see Chapter I 4) as well as research questions 4a and 4b (see Chapter I 5) are addressed together.

## I 3 Research question 2: patients who are not candidates for local therapy

### I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on relugolix (status: 3 August 2022)
- bibliographical literature search on relugolix (last search on 3 August 2022)
- search in trial registries/trial results databases for studies on relugolix (last search on 24 August 2022)
- search on the G-BA website for relugolix (last search on 3 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on relugolix (last search on 24 October 2022), for search strategies, see I Appendix A of the full dossier assessment

The check of the study pool identified study C27002 [3,4] in addition to study MVT-601-3201 (HERO), which was used by the company and included in the benefit assessment.

**Study C27002**

The company identified the C27002 study, but excluded it from the study pool. It justified the exclusion by stating that the study excluded patients with symptomatic disease with advanced (N1) or metastatic (M1) prostate cancer.

The inclusion criteria of the C27002 study largely correspond to those of the HERO study, which the company included for the benefit assessment. Study C27002 included patients with advanced hormone-sensitive prostate cancer who met one of the following criteria: a) advanced localized disease and primary therapy not suitable, b) evidence of PSA biochemical or clinical relapse following primary intervention (surgery or radiation therapy) of curative intent, or c) newly diagnosed asymptomatic metastatic disease. The study compared relugolix (2 intervention arms with different doses) with leuprorelin. In one of the 2 relugolix arms, the dosing was in compliance with the approval except for the starting dose on day 1 (320 mg instead of 360 mg) [5].

In the C27002 study, at least the results of the patients with non-metastatic prostate cancer are potentially relevant for research question 2 of the present benefit assessment. However, according to information in the clinical study report (CSR), this concerns a maximum of 17 versus 17 patients. Due to the small number of patients in comparison with the subpopulation of the HERO study used for research question 2 (see Section I 3.1.2.2), it is assumed that the

influence on the results of the present benefit assessment is small. Study C27002 is therefore not considered further in the dossier assessment.

### I 3.1.1 Study included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: relugolix vs. leuprorelin

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Study for the approval 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 and other sources[c] (yes/no [citation]) |
| MVT-601-3201 (HERO[d]) | Yes | No | Yes[e] | Yes [6,7] | Yes [8,9] | Yes [10,11] |

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. The company took over the approval for relugolix from the study sponsor Myovant Sciences Ltd. in 2022.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The company used a subpopulation of the HERO study to assess the added benefit of relugolix in patients with advanced hormone-sensitive prostate cancer who are not candidates for local therapy.

The section below describes the study and the subpopulation relevant for the benefit assessment.

### I 3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: relugolix vs. leuprorelin

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| HERO | RCT, open-label, parallel | Adults (≥ 18 years) with advanced hormone-sensitive prostate cancer and ECOG PS 0 or 1 with one of the following criteria:<br>▪ evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, and not a candidate for salvage treatment by surgery, or<br>▪ newly diagnosed, metastatic disease, or<br>▪ advanced localized disease that is unlikely to be cured with local primary intervention (surgery or radiation) with curative intent | Relugolix (N = 719)<br>Leuprorelin (N = 359)<br><br>Relevant subpopulation thereof[b]:<br>relugolix (n = 427)<br>leuprorelin (n = 213) | Screening: 28 days<br><br>Treatment: maximum of 48 weeks or until unacceptable toxicity, dose interruption of relugolix > 10 days, or withdrawal of consent<br><br>Observation[c]: outcome-specific, at most until death, lost to follow-up or withdrawal of informed consent | 160 centres in: Australia, Austria, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, New Zealand, Poland, Slovakia, South Korea, Spain, Sweden, Taiwan, United Kingdom, USA<br><br>4/2017–11/2021[d]<br><br>Data cut-offs[e]:<br>▪ 10 December 2019f<br>▪ 23 September 2020g | Primary: sustained testosterone suppression at castrate level<br>Secondary: overall survival, symptoms, health-related quality of life, AEs |

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Patients without distant metastasis (M0).
c. Outcome-specific information is provided in Table 8.
d. Due to the inclusion of further patients in China, the study was continued after the final analysis (September 2020) until the end of the study (November 2021).
e. Only data at the database lock are available in each case.
f. Prespecified primary analysis.
g. Prespecified final analysis.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; PSA: prostate-specific antigen; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: relugolix vs. leuprorelin

| Study | Intervention | Comparison |
|---|---|---|
| HERO | Relugolix, oral:<br>▪ Day 1: 360 mg<br>▪ From day 2 up to a maximum of 48 weeks: 120 mg daily | Leuprorelin, subcutaneous, as depot:<br>▪ 11.25 mg in Japan, Taiwan and China<br>▪ 22.5 mg in all other countries<br>▪ every 12 weeks up to a maximum of 48 weeks[a]<br><br>An antiandrogen could be administered for the first 4 weeks or longer if indicated, as determined by the investigator[b]. |
| | **Dose adjustment**<br>▪ Dose escalation and dose reduction were not allowed[c]<br>**Concomitant treatment[d]**<br>▪ palliative radiation to sites other than the prostate<br>▪ no sooner than 2 months after initiation of treatment: supplementary radiotherapy, cryotherapy or high frequency ultrasound<br>▪ enzalutamide was allowed after confirmed PSA progression[e] | |
| | **Non-permitted pretreatment**<br>▪ GnRH analogues or other form of ADT (oestrogen or antiandrogen) with a treatment duration > 18 months[f]<br>▪ systemic cytotoxic treatment for prostate cancer (e.g. taxane-based regimen)<br>▪ surgical castration<br>**Non-permitted concomitant treatment[g]**<br>▪ GnRH analogues or other forms of ADT, CYP17 inhibitors (e.g. abiraterone)<br>▪ class IA and class III antiarrhythmics<br>▪ moderate to strong CYP3A inducers<br>▪ moderate to strong P-glycoprotein inducers and inhibitors<br>▪ High-dose biotins<br>▪ herbal preparations (e.g. ginkgo biloba, kava kava) | |

a. The last injection was given 12 weeks before the end of treatment (i.e. at week 37).
b. According to the approval of leuprorelin, additional administration of an appropriate antiandrogen should be considered beginning 3 days prior to leuprorelin therapy and continuing for the first 2 to 3 weeks of treatment due to the temporary rise in serum testosterone [12].
c. Treatment interruption for ≤ 10 consecutive days due to toxicities (grade ≥ 3 related to study medication) was possible for relugolix, otherwise treatment was discontinued.
d. Patients with disease progression, in the presence of testosterone suppression below castrate levels (≤ 50 ng/dL), were encouraged to remain on study drug and, if indicated, receive radiotherapy.
e. If other systemic antineoplastic therapy was required, the medical monitor had to be contacted.
f. If the treatment duration was ≤ 18 months, then that therapy must have been completed at least 3 months prior to baseline.
g. Patients who, in the investigator's opinion, were likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating study treatment were excluded from the HERO study.

ADT: androgen deprivation therapy; CYP: cytochrome P450; GnRH: gonadotropin-releasing hormone; PSA: prostate-specific antigen; RCT: randomized controlled trial

#### I 3.1.2.1 Study design

The HERO study is an open-label RCT comparing relugolix with leuprorelin in patients with advanced hormone-sensitive prostate cancer. Patients had to be candidates for, in the opinion of the investigator, at least 1 year of ADT for the treatment of advanced hormone-sensitive prostate cancer. Patients whose disease fulfilled one of the following criteria were included:

- evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, and not a candidate for salvage treatment by surgery (hereafter referred to as “Group A”), or
- newly diagnosed metastatic disease (hereafter referred to as “Group B”), or
- advanced localized disease that is unlikely to be cured with local primary intervention (surgery or radiation) with curative intent (hereafter referred to as “Group C”).

Patients were not allowed to have a history of surgical castration. Also, patients were not allowed to have previously been treated with a GnRH analogue or another form of ADT (oestrogen or anti-androgen) for more than 18 months. If the treatment duration was ≤ 18 months, then that therapy must have been completed at least 3 months prior to baseline. Enrolment was limited to patients with ECOG PS ≤ 1.

A total of 1078 patients were randomly allocated in a 2:1 ratio to treatment with relugolix (N = 719) or leuprorelin (N = 359). Randomization was stratified by region (North and South America/Europe/Asia and other regions), the presence of metastatic prostate cancer (yes/no) and age at baseline (≤ 75/> 75 years).

Treatment with relugolix was given as a daily oral dose (360 mg on day 1, 120 mg from day 2 onwards) in compliance with the SPC [5].

Leuprorelin was administered as subcutaneous depot injection every 12 weeks. Treatment with 11.25 mg leuprorelin in Japan, Taiwan and China, and with 22.5 mg leuprorelin in the other countries, was in compliance with the respective SPCs [12,13]. An antiandrogen could be administered for the first 4 weeks or longer if indicated, as determined by the investigator, which is largely in compliance with the SPC.

Treatment was given in both study arms for a maximum of 48 weeks or until unacceptable toxicity, dose interruption of relugolix > 10 days, or withdrawal of consent. Supplementary radiotherapy, cryotherapy or high frequency ultrasound was allowed no sooner than 2 months after initiation of treatment. However, palliative radiation to sites other than the prostate was permitted at earlier time points.

The primary outcome of the study was sustained testosterone suppression at castrate level. Patient-relevant secondary outcomes were overall survival, outcomes on morbidity, health-related quality of life, and AEs.

#### I 3.1.2.2 Relevant subpopulation

The company used a subpopulation of patients in the HERO study for research question 2 (patients who are not candidates for local therapy; no distant metastasis).

The subpopulation from the HERO study includes, firstly, those patients in Group A (biochemical or clinical relapse following local primary intervention with curative intent; not candidates for salvage treatment by surgery) who have no distant metastases. Secondly, it includes all patients in Group C. These are patients with advanced localized disease that is unlikely to be cured with local primary intervention (surgery or radiation) with curative intent. In total, 427 patients in the intervention arm and 213 patients in the comparator arm belong to this subpopulation.

From the point of view of the company, with this subpopulation, only patients are considered who, in the opinion of the investigator, were no longer candidates for local therapy at the time of study inclusion.

The inclusion criteria of the HERO study show that patients in Group A are not candidates for salvage treatment by surgery, and that patients in Group C are not candidates for surgery or radiation. Beyond that, however, no concrete criteria were defined to operationalize the suitability of local therapies. Despite this uncertainty, it is assumed that the patients in Group C and those in Group A were no longer eligible for the therapies mentioned in each case.

However, for an unknown proportion of patients in the subpopulation analysed by the company, there is uncertainty as to whether local therapy or, specifically, salvage radiotherapy would still have been an option for them. In the subpopulation of the company, this only concerns patients from Group A. For Group C, it can be assumed on the basis of the inclusion criterion of the HERO study (unlikely to be cured with local primary intervention with curative intent) that these patients would not have been candidates for local therapy.

The inclusion criterion for Group A of the HERO study (patients with recurrence, not a candidate for salvage treatment by surgery) defined that surgery was no longer an option for the patients. However, the inclusion criterion did not indicate whether local salvage radiotherapy would still have been an option for these patients.

Rather, according to the study documents, it is assumed that non-palliative radiotherapy (at least in addition to an ADT) could still be an option for the patients. Thus, in the study – in

addition to palliative radiotherapy – radiotherapy in the non-palliative setting was also allowed 2 months after the start of the study treatment. In the subpopulation presented by the company, a total of approximately 20% of the patients received (palliative or non-palliative) radiation during the course of the study. The information in the study documents shows that a proportion of 17.5% of the patients in the subpopulation received radiotherapy in the primary or salvage setting during the course of the study.

Based on the information in the dossier on prior radiotherapy in patients in the HERO study, it is assumed that the proportion of patients in the subpopulation of the company who would still have been potential candidates for local salvage radiotherapy was no more than 27%[4].

It should be noted that guidelines recommend salvage radiotherapy for PSA recurrence to be performed as early as possible after recurrence up to a PSA value of 0.5 ng/mL because the curative potential is notably lower or lost above this value [14,15]. Furthermore, in addition to the PSA value, other criteria such as the patient's age, concomitant diseases and life expectancy must be taken into account when deciding on salvage radiotherapy [14]. It can therefore be assumed that, due to the restrictions mentioned, and the narrow PSA range in particular, radiotherapy was not indicated for all patients within the 27% proportion. However, data on the PSA value or the above-mentioned characteristics are not available for the patient group without prior radiotherapy. In the dossier, the company could have presented corresponding characteristics or reasons that guided the investigator in assessing whether patients were still candidates for local radiotherapy.

Overall, the exact proportion of patients who were still candidates for radiotherapy cannot be quantified. No information, e.g. in the form of subgroup analyses, is available on the extent to which the characteristic of candidate for local therapy influenced the effects observed in the subpopulation. In the present situation, however, it is assumed that the proportion of patients who were candidates for local therapy is within a range that allows the subpopulation of the company to be used for the research question of patients who are not candidates for local therapy. Furthermore, according the European Public Assessment Report (EPAR) [11], the regulatory authority also assumes – albeit without justification – that all patients in the HERO study were not candidates for surgery or radiotherapy with curative intent.

[4] The calculation is based on the following assumption: In Group C (unlikely to be cured with local primary intervention), no radiotherapies have yet been performed, i.e. prior radiotherapies in the subpopulation of the company can all be assigned to patients in Group A (with recurrence). 209 patients in the subpopulation of the company had prior radiotherapy. Thus, of the 384 patients in Group A in the subpopulation of the company, 209 had prior radiotherapy and 175 had no prior radiotherapy. For 175/640 (27%) patients in the subpopulation of the company, radiotherapy was therefore potentially still an option.

In the overall assessment, the uncertainty as to whether all patients in the subpopulation presented by the company were no longer candidates for local therapy is taken into account in the certainty of conclusions.

**Note on leuprorelin dosing in the relevant subpopulation**

Patients in the comparator arm of the relevant subpopulation received leuprorelin every 12 weeks. Leuprorelin was used at a dose of 22.5 mg in 177 (83.1%) of the patients. Patients in Japan, Taiwan and China (16.9%) received leuprorelin at a dose of 11.25 mg. Both dosages of leuprorelin are in compliance with the approval [12,13].

#### I 3.1.2.3 Data cut-offs

A primary and a final analysis were prespecified in the HERO study; the respective database locks were on 10 December 2019 and 23 September 2020. The final analysis was planned after approximately 390 patients with metastatic disease had been randomized and patients had either completed the 48-week study treatment, including the follow-up visit 30 days after the end of treatment, or had discontinued the study. In Module 4 A, the company presented results for the final analysis with database lock on 23 September 2020. The company did not provide any information on the date of the data cut-off. The results of the final data cut-off are used in the present benefit assessment.

#### I 3.1.2.4 Planned duration of follow-up observation

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

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

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **HERO** | |
| Mortality | |
| Overall survival | ▪ Until death, lost to follow-up, or withdrawal of informed consent |
| Morbidity | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25) and health status (EQ-5D VAS) | ▪ 30 days after treatment end[a] |
| Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25) | ▪ 30 days after treatment end[a] |
| Side effects | |
| AEs/SAEs | ▪ Until 30 days after treatment end[a] or until initiation of a subsequent therapy (whichever occurred first) |
| a. Day of last dose of relugolix or 12 weeks after last injection of leuprorelin.<br>AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale | |

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

### I 3.1.2.5 Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients in the relevant subpopulation of the included study.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: relugolix vs. leuprorelin (multipage table)

| **Study**<br>**Characteristic**<br>**Category** | **Relugolix**<br>**N = 427** | **Leuprorelin**<br>**N = 213** |
|---|---|---|
| **HERO** | | |
| Age [years], mean (SD) | 71 (8) | 71 (8) |
| Family origin, n (%) | | |
| Asian | 94 (22) | 51 (24) |
| Black or African American | 21 (5) | 12 (6) |
| White | 292 (68) | 139 (65) |
| Other | 7 (2) | 4 (2) |
| Diverse | 7 (2) | 3 (1) |
| Unknown | 6 (1) | 4 (2) |
| Region | | |
| North America | 138 (32) | 69 (32) |
| South America | 23 (5) | 11 (5) |
| Europe | 155 (36) | 78 (37) |
| Asia | 93 (22) | 50 (23) |
| Other regions | 18 (4) | 5 (2) |
| ECOG PS, n (%) | | |
| 0 | 378 (89) | 191 (90) |
| 1 | 49 (11) | 22 (10) |
| Disease duration: time since first diagnosis [years], median [min; max] | 1.5 [0.0; 21.7] | 1.6 [0.1; 30.7] |
| Clinical disease state | | |
| Group A: no distant metastases; biochemical (PSA) or clinical relapse following primary intervention with curative intent, and not a candidate for salvage treatment by surgery | 253 (59) | 131 (62) |
| Group B: newly diagnosed, metastatic disease | 0 (0) | 1 (< 1)[a] |
| Group C: advanced localized disease that is unlikely to be cured with local primary intervention (surgery or radiation) | 174 (41) | 81 (38) |
| Disease stage[b], n (%) | | |
| Metastatic (M1) | 0 (0) | 0 (0) |
| Locally advanced | 192 (45) | 96 (45) |
| Localized | 178 (42) | 83 (39) |
| Not classifiable | 57 (13) | 34 (16) |
| Gleason score, n (%) | | |
| ≤ 6 | 74 (17)[c] | 36 (17)[c] |
| 7 | 178 (42) | 100 (47) |
| 8-10 | 163 (38) | 74 (35) |
| Unknown | 12 (3) | 3 (1.4) |

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: relugolix vs. leuprorelin (multipage table)

| **Study**<br>**Characteristic**<br>**Category** | **Relugolix**<br>**N = 427** | **Leuprorelin**<br>**N = 213** |
|---|---|---|
| PSA concentration [ng/mL], median [min; max] | 8.1 [0.2; 972.3] | 6.2 [0.2; 484.6] |
| Testosterone concentration [ng/dL], median [min; max] | 429 [142; 1183] | 393 [119; 1267] |
| Prior ADT[d], n (%) | 60 (14) | 22 (10) |
| Prior radiotherapy, n (%) | 137 (32) | 72 (34) |
| Prior prostatectomy, n (%) | 183 (43) | 104 (49) |
| Treatment discontinuation, n (%)[e] | 29 (7) | 19 (9) |
| Study discontinuation, n (%)[f] | 29 (7) | 19 (9) |

a. The relevant subpopulation of the company also includes one patient with newly diagnosed, metastatic prostate cancer (Group B of the HERO study). The company did not specify why this patient is part of the relevant subpopulation of patients with non-metastatic prostate cancer.
b. Based on TNM status at baseline: metastatic: M1; locally advanced: T3/4 NX M0 or N1 M0 and any T N1 M0; localized: T1 or T2 N0 M0.
c. Institute's calculation.
d. Patients with surgical castration were excluded from the study.
e. Calculated from the data provided by the company on the number of patients who completed the treatment.
f. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): adverse event (2.8% vs. 1.9%), patient request (1.4% vs. 1.4%) and other reasons (1.6% vs. 4.2%).

ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; PSA: prostate-specific antigen; RCT: randomized controlled trial; SD: standard deviation; TNM: classification by primary tumour, lymph node involvement, distant metastases

The characteristics of the HERO study's subpopulation relevant for the assessment are largely comparable between the 2 treatment arms. The mean age of the patients was 71 years. Over 2 thirds of all patients came from Europe or North America, and just over 20% from Asia. About 90% of patients had an ECOG PS of 1. 60% of patients in the relevant subpopulation had recurrent disease (Group A), 40% had advanced, localized disease unlikely to be cured with local primary intervention (Group C).

The proportion of patients who discontinued treatment or the study was less than 10% in both study arms.

### I 3.1.2.6 Information on the course of the study

Table 10 shows the mean and median treatment duration of the patients.

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

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Relugolix**<br>**N = 427** | **Leuprorelin**<br>**N = 213** |
|---|---|---|
| **HERO** | | |
| Treatment duration [weeks] | | |
| Median [min; max] | 48, 0 [0.4; 51.4] | 48.1 [9.1; 51.6] |
| Mean (SD) | 46.5 (7.4) | 46.4 (6.6) |
| Observation period [months] | | |
| Overall survival | ND | ND |
| Morbidity | ND | ND |
| Health-related quality of life | ND | ND |
| Side effects | ND | ND |

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median and mean treatment durations are comparable between the treatment arms and were about 48 and 46 weeks respectively. There is no information on the observation period for any of the patient-relevant outcomes. For outcomes in the morbidity, health-related quality of life, and side effects outcome categories, the observation period was linked to treatment end (see Table 8). Therefore, it is safe to assume that, for these outcomes, the observation duration is shortened with respect to overall survival.

#### I 3.1.2.7 Subsequent therapies

No data on subsequent therapies are available for either the total population or the relevant subpopulation of the HERO study. Information on subsequent therapies is generally required for the benefit assessment, especially for the assessment of results on outcomes that were observed beyond the end of treatment.

#### I 3.1.2.8 Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: relugolix vs. leuprorelin

| 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 | | | |
| HERO | Yes | Yes | No | No | Yes | Yes | Low |
| RCT: randomized controlled trial | | | | | | | |

The risk of bias across outcomes is rated as low for the HERO study.

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

### I 3.1.3 Transferability of the study results to the German health care context

The company stated that the HERO study was mainly conducted in North and South America, Asia and Europe, and that 37.8% of patients in European centres and 28.9% of patients in North American centres participated in the study. According to the company, the health care context of these regions is comparable to the German health care standard, so that transferability was assumed for about 2 thirds of the study population. From the point of view of the company, a similar picture emerges in the separate consideration of the relevant subpopulation. The company added that the subgroup analysis for the characteristic of region did not show any effect modifications with regard to all patient-relevant outcomes, and that the study participants' average age of 71 years in both the total population and the relevant subpopulation corresponded to the mean age at disease onset in Germany in 2018. The company also stated that the treatment regimen of relugolix and leuprorelin in the HERO study corresponded to the dosage approved in Germany, and that leuprorelin was also the testosterone suppression drug most commonly used in practice, so that the HERO study compared relugolix with the current standard of ADT. Hence, the company considered the results of the HERO study to be transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

## I 3.2 Results on added benefit

### I 3.2.1 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 EORTC QLQ-PR25
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-PR25
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 12 shows for which outcomes data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: relugolix vs. leuprorelin

| Study | Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-PR25) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25) | SAEs | Severe AEs[a] | Discontinuation due to AEs | Specific AEs |
| HERO | Yes | No[b] | Yes | No[b] | Yes | Yes | Yes | No[c] |

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The company did not provide the required analyses with a response criterion of ≥ 10 points (see text below the table for reasoning).
c. No specific AEs identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

**Analyses on the EORTC QLQ-C30 and EORTC QLQ-PR25**

The company presented responder analyses for the time to deterioration by ≥ 15 points for the relevant subpopulation for the results using the EORTC QLQ-C30 and the EORTC QLQ-PR25. 15 points correspond to 15% of the scale range for all scales of both instruments (with a range 0 to 100). According to the "Answers to frequently asked questions about the benefit assessment procedure" [16] provided by the G-BA, only analyses of the currently accepted minimally important difference (MID) of 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules.

Depending on the scale, a response criterion of ≥ 15 points may lead to a different number of responders compared with the response criterion of ≥ 10 points (see dossier assessment A22-40 using the example of the EORTC QLQ-C30 [17]). In the present situation, in addition to few scales of the EORCT QLQ-C30, this concerns the EORTC QLQ-PR25 scale on micturition problems, for example. For example, for this 8-item scale, a response threshold of 10 points corresponds to a change step of 3 points on one item of the scale (12.5 points), while a response threshold of 15 points requires a change step of 4 points (16.7 points). In such cases, if the response criterion is changed from ≥ 15 to ≥ 10 points, changes in statistical significance are possible if the associated p-value (using the 15 points) is close to the significance level

(above or below the 0.05 level). In the present dossier assessment, this is the case for the scale of micturition problems (p = 0.072, see I Appendix B of the full dossier assessment), for example. Overall, the dossier assessment requires analyses on the previously accepted response threshold of 10 points.

The results of all scales of the EORTC QLQ-C30 and EORTC QLQ PR-25 with a response criterion of ≥ 15 points provided by the company are presented as supplementary information in Appendix B of the full dossier assessment.

**Major adverse cardiovascular events**

In its dossier, the company presented the outcome of major adverse cardiovascular event (MACE) and assigned it to the outcome category of morbidity. In Module 4 A, the outcome was defined as a composite outcome with the following individual components:

- any event leading to death
- "nonfatal myocardial infarction", recorded using the Standardized Medical Dictionary for Regulatory Activities Query (SMQ) "myocardial infarction" (broad) excluding fatal events
- "nonfatal central nervous system (CNS) haemorrhages and cerebrovascular conditions", recorded using the SMQ "central nervous system haemorrhages and cerebrovascular conditions" (broad) excluding fatal events

The company also presented results of a sensitivity analysis in which the component "any event leading to death" was replaced by the component "cardiovascular events leading to death". In addition to the results for the composite outcome, the company also presented the results of the 3 individual components.

The company stated that the outcome was prespecified. It should be noted that although the outcome was not defined as an outcome in the study protocol, the statistical analysis plan (SAP) listed various categories of AEs, including, among others, the category "adverse cardiovascular events". Cardiovascular events are specified in this category using the recording of MACE (SMQ "myocardial infarction" [broad], SMQ "central nervous system haemorrhages and cerebrovascular conditions" [broad], death due to all causes) and ischaemic heart disease (SMQ "ischaemic heart disease" [broad]). Thus, the recording of MACE events – even if not explicitly named as an outcome – is to be considered predefined in the context of the AE recording using events leading to death as well as events recorded using the mentioned SMQs. However, it should be critically noted that the SAP also defined additional SMQs, for example the aforementioned SMQ "ischaemic heart disease" or the SMQ "osteoporosis/osteopenia", the results of which are not presented by the company for the relevant subpopulation in its dossier.

The outcome of MACE is not used for the present benefit assessment for the following reasons:

Based on the available information in the dossier, it cannot be assessed whether the outcome of MACE – in the sense of severe or serious cardiovascular or cerebrovascular events – is represented with sufficient measurement reliability with the operationalization described. Firstly, there is no information on the events that were included in the individual components "nonfatal myocardial infarction" and "nonfatal CNS haemorrhages and cerebrovascular conditions" in the subpopulation presented. The data for the total population of the HERO study show that the few events that occurred anyway included some events that cannot necessarily be attributed to MACE events. An example is the Preferred Term (PT) "troponin increased". Secondly, there is also a lack of information on the respective severity grade of the recorded events, which is necessary for the assessment of a MACE event. It is thus unclear whether all events included in the analyses of the relevant subpopulation actually represent severe or serious cardiovascular events in the sense of a MACE. For this purpose, MACE outcomes usually include an adjudication of the events included in the outcome. In the HERO study, however, no such adjudication took place. This was also criticized by the regulatory authority in the EPAR [11].

Overall, the operationalization of the outcome of MACE, together with the unclear measurement reliability, is not suitable for representing patient-relevant severe or serious cardiovascular events. Due to the described points of criticism, the outcome is not used in the benefit assessment.

Regardless of this, the outcome would have to be assigned to the outcome category of side effects if it were operationalized appropriately. Irrespective of the points of criticism described regarding the outcome of MACE, there are no notable differences in cardiovascular events between the treatment groups based on common AEs, SAEs, severe AEs or discontinuations due to AEs (see I Appendix D of the full dossier assessment).

### I 3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: relugolix vs. leuprorelin

| Study | Study level | Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-PR25) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-PR25) | SAEs | Severe AEs[a] | Discontinuation due to AEs | Specific AEs |
| HERO | L | L | –[b] | H[c] | –[b] | L | L | H[d] | – |

a. Operationalized as CTCAE grade ≥ 3.
b. The company did not provide the required analyses with a response criterion of ≥ 10 points (see Section I 3.2.1 for reasoning).
c. Lack of blinding in subjective recording of outcomes as well as unclear proportion of patients included in the analysis.
d. Lack of blinding in subjective decision-making on discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias of the results for the outcomes of overall survival, SAEs and severe AEs is rated as low.

The risk of bias of the results for the symptom and health-related quality of life outcomes recorded using the EORTC QLQ-C30 and EORTC QLQ-PR25 is not assessed, as the company did not provide the required analyses with a response criterion of ≥ 10 points (see Section I 3.2.1 for reasoning).

The risk of bias of the results for the outcome of health status, recorded with the EQ-5D VAS, is rated as high due to the lack of blinding in subjective recording of outcomes and due to the unclear proportion of patients included in the analysis. According to the company, all patients in the relevant subpopulation were included in the analyses of the patient-reported outcomes. At the same time, however, the company stated that patients with no baseline value and/or no value in the further course of the study were censored on day 1. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be determined. Based on the information on the responses to the EQ-5D VAS, the number of

patients included in the analysis is considered to be sufficiently large for the analysis to be used for the benefit assessment.

The risk of bias for the outcome of discontinuation due to AEs is rated as high because of lack of blinding with subjective decision on discontinuation.

### I 3.2.3 Results

Table 14 and Table 15 summarize the results on the comparison of relugolix with leuprorelin for research question 2 of the present benefit assessment. 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 event time analyses are presented in I Appendix C of the full dossier assessment, and the results on common AEs, SAEs, and severe AEs as well as discontinuation due to AEs are presented in I Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: relugolix vs. leuprorelin

| Study<br>Outcome category<br>Outcome | Relugolix<br>N | Relugolix<br>Median time to event in months [95% CI][a]<br>Patients with event n (%) | Leuprorelin<br>N | Leuprorelin<br>Median time to event in months [95% CI][a]<br>Patients with event n (%) | Relugolix vs. leuprorelin<br>HR [95% CI]; p-value[b] |
|---|---|---|---|---|---|
| **HERO** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 427 | NA<br>3 (0.7) | 213 | NA<br>4 (1.9) | 0.36 [0.08; 1.62]; 0.185 |
| **Morbidity** | | | | | |
| EORTC QLQ-C30 and EORTC QLQ-PR25 – symptom scales | Required analyses with response criterion of ≥ 10 points are missing[c] | | | | |
| Health status | | | | | |
| EQ-5D VAS[d] | ND[e] | NA<br>107 (25.1[f]) | ND[e] | 11.5 [11.3; NC]<br>60 (28.2[f]) | 0.89 [0.65; 1.22]; 0.465 |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 and EORTC QLQ-PR25 | Required analyses with response criterion of ≥ 10 points are missing[c] | | | | |

a. Institute's conversion from time data to months.
b. HR, CI and p-value: Cox proportional hazards model; stratified by region (North and South America/Europe/Asia/other regions) and age (≤ 75 years/> 75 years).
c. The company presented responder analyses for the time to deterioration by ≥ 15 points for the relevant subpopulation for the EORTC QLQ-C30 and the EORTC QLQ-PR25. According to the "Answers to frequently asked questions about the benefit assessment procedure" [16] provided by the G-BA, only analyses of the currently accepted MID of 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules (see Section I 3.2.1 for reasoning).
d. Time to first deterioration. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
e. According to the company, all patients of the relevant subpopulation were included in the analysis. At the same time, the company stated that patients with no baseline value and/or no value in the course of the study were censored on day 1. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be calculated. Based on the information on the responses, the number of patients included in the analysis is considered to be sufficiently large.
f. Percentage refers to the number of patients randomized into this arm.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MID: minimally important difference; 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; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; VAS: visual analogue scale

Table 15: Results (side effects) – RCT, direct comparison: relugolix vs. leuprorelin

| Study<br>Outcome category<br>Outcome | Relugolix<br>N | Relugolix<br>Patients with event<br>n (%) | Leuprorelin<br>N | Leuprorelin<br>Patients with event<br>n (%) | Relugolix vs. leuprorelin<br>RR [95% CI][a];<br>p-value[b] |
|---|---|---|---|---|---|
| **HERO** | | | | | |
| **Side effects** | | | | | |
| AEs (supplementary information) | 427 | 396 (92.7) | 213 | 201 (94.4) | – |
| SAEs | 427 | 40 (9.4) | 213 | 27 (12.7) | 0.74 [0.47; 1.17]; 0.204 |
| Severe AEs[c] | 427 | 64 (15.0) | 213 | 35 (16.4) | 0.91 [0.63; 1.33]; 0.736 |
| Discontinuation due to AEs | 427 | 12 (2.8) | 213 | 1 (0.5) | 5.99 [0.78; 45.73]; 0.0502 |

a. RR, CI (asymptotic); unstratified.
b. p-value: Institute's calculation (unconditional exact test, CSZ method according to [18]).
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Based on the available information, at most hints, e.g. of an added benefit, can be derived for all outcomes (see Section I 3.1.2.2 and Section I 3.2.2 for reasoning).

### Mortality

#### *Overall survival*

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

### Morbidity

#### *Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25)*

The required analyses with a response criterion of ≥ 10 points are not available for the symptom outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25 (see Section I 3.2.1 for reasoning). In each case, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven. The results of all scales of the EORTC QLQ-C30 and EORTC QLQ PR-25 with a response criterion of ≥ 15 points provided by the company are presented as supplementary information in I Appendix B of the full dossier assessment.

#### *Health status (EQ-5D VAS)*

Health status was surveyed by EQ-5D VAS. The time to deterioration by ≥ 15 points was used.

No statistically significant differences between treatment groups were found for the outcome of health status. There is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven.

**Health-related quality of life**

***EORTC QLQ-C30 and EORTC QLQ-PR25***

The required analyses with a response criterion of ≥ 10 points are not available for the health-related quality of life outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25 (see Section I 3.2.1 for reasoning). In each case, there is no hint of an added benefit of relugolix in comparison with leuprorelin; an added benefit is therefore not proven. The results of all scales of the EORTC QLQ-C30 and EORTC QLQ PR-25 with a response criterion of ≥ 15 points provided by the company are presented as supplementary information in I Appendix B of the full dossier assessment.

**Side effects**

***SAEs, severe AEs, discontinuation due to AEs***

There were no statistically significant differences between treatment groups for the outcomes of SAEs, severe AEs and discontinuation due to AEs. There is no hint of greater or lesser harm from relugolix in comparison with leuprorelin for any of them; greater or lesser harm is therefore not proven.

***Specific AEs***

No specific AEs were selected. Information on the MACE outcome provided by the company can be found in Section I 3.2.1.

### I 3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present benefit assessment:

- age (< 75 years, ≥ 75 years)
- Gleason score at baseline (< 8 vs. ≥ 8)

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.

For binary outcomes, the company's interaction test was based on the odds ratio and not on the relative risk. Especially in the case of higher risks for an event, this can lead to differences in the results. For this reason, an interaction test on the basis of the relative risks using a Q test was subsequently performed for the present assessment, provided that the company's analysis had produced a statistically significant effect modification to the level of 0.2. No

qualitative difference between the test results on the basis of the odds ratios and of the relative risks were shown. The test results presented by the company were therefore used.

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

Subgroup analyses are available for all outcomes included. When applying the above-described methods, no effect modifications are shown.

### I 3.3 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 [1].

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 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 16).

Table 16: Extent of added benefit at outcome level: relugolix vs. leuprorelin

| **Outcome category**<br>**Outcome** | **Relugolix vs. leuprorelin**<br>**Median time to event (months) or proportion of events (%)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Total observation period** | | |
| **Mortality** | | |
| Overall survival | NA vs. NA<br>HR: 0.36 [0.08; 1.62]; p = 0.185 | Lesser/added benefit not proven |
| **Shortened observation period** | | |
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-PR25) | Required analyses with response criterion of ≥ 10 points are missing[c] | Lesser/added benefit not proven |
| Health status (EQ--5D VAS) – deterioration ≥ 15 points | | |
| EQ-5D VAS | NA vs. 11.5<br>HR: 0.89 [0.65; 1.22]; p = 0.465 | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 and EORTC PR-25 | Required analyses with response criterion of ≥ 10 points are missing[c] | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs | 9.4% vs. 12.7%<br>RR: 0.74 [0.47; 1.17]; p = 0.204 | Greater/lesser harm not proven |
| Severe AEs | 15.0% vs. 16.4%<br>RR: 0.91 [0.63; 1.33]; p = 0.736 | Greater/lesser harm not proven |
| Discontinuation due to AEs | 2.8% vs. 0.5%<br>RR: 5.99 [0.78; 45.73]; p = 0.0502 | Greater/lesser harm not proven |

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 company presented responder analyses for the time to deterioration by ≥ 15 points for the relevant subpopulation for the EORTC QLQ-C30 and the EORTC QLQ-PR25. According to the "Answers to frequently asked questions about the benefit assessment procedure" [16] provided by the G-BA, only analyses of the currently accepted MID of 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules (see Section I 3.2.1 for reasoning).

AE: adverse event; CI: confidence interval; $CI_u$: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MID: minimally important difference; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

### I 3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of relugolix in comparison with leuprorelin

| **Positive effects** | **Negative effects** |
|---|---|
| **Total observation period** | |
| – | – |
| **Shortened observation period** | |
| – | – |
| The required analyses with a response criterion of ≥ 10 points are not available for the outcomes on symptoms and health-related quality of life. | |

Overall, neither positive nor negative effects were found. The company did not provide the required analyses with a response criterion of ≥ 10 points for the symptom and health-related quality of life outcomes recorded with the EORTC QLQ-C30 and EORTC QLQ-PR25. When looking at the results with a response criterion of ≥ 15 points, there is no statistically significant difference between the treatment groups in any scale, except for a no more than marginal effect in the diarrhoea scale of the EORTC QLQ-C30. For the EORTC QLQ-PR25 scale on micturition problems, there may be a negative effect if the response criterion of ≥ 10 points is applied.

In summary, there is no added benefit of relugolix in comparison with the ACT for patients with advanced hormone-sensitive prostate cancer who are not candidates for local therapy.

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

## I 4 Research questions 1 and 3: patients who are candidates for local therapy, and patients with PSA recurrence or clinical recurrence after primary local therapy

### I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on relugolix (status: 3 August 2022)
- bibliographical literature search on relugolix (last search on 3 August 2022)
- search in trial registries/trial results databases for studies on relugolix (last search on 24 August 2022)
- search on the G-BA website for relugolix (last search on 3 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on relugolix (last search on 24 October 2022), for search strategies, see I Appendix A of the full dossier assessment

For the benefit assessment, the company identified the HERO study for all research questions (see Section I 3.1.1).

**Research question 1**

The company stated that no relevant data from the HERO study were available for the assessment of the added benefit of relugolix for patients who are candidates for local therapy (research question 1). The assessment of the company is appropriate.

**Research question 3**

The company stated that no relevant data from the HERO study were available for the assessment of the added benefit of relugolix for patients with PSA recurrence or clinical recurrence after primary local therapy (research question 3).

For patients with recurrence, the G-BA specified local therapy, if indicated in combination with conventional ADT or bicalutamide, taking into account the prior therapy and the risk of progression, as ACT. As explained in Section I 3.1.2.2, it can be assumed that local therapy, in this case salvage radiotherapy, would still have been an option for an unknown, albeit small, proportion of patients with recurrence in the HERO study (Group A). These patients would have to be assigned to research question 3 of the present benefit assessment.

The company's assessment that no data relevant to the benefit assessment are available for research question 3 is appropriate insofar as leuprorelin was not an implementation of the

ACT for the proportion of patients in the HERO study who would have still been potential candidates for local therapy.

### I 4.2 Results on added benefit

The company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with advanced hormone-sensitive prostate cancer who are candidates for local therapy (research question 1), and patients with PSA recurrence or clinical recurrence after primary local therapy (research question 3). This results in no hint of added benefit of relugolix in comparison with the ACT for research question 1 or research question 3; an added benefit is therefore not proven.

### I 4.3 Probability and extent of added benefit

Since the company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with advanced hormone-sensitive prostate cancer who are candidates for local therapy (research question 1), and patients with PSA recurrence or clinical recurrence after primary local therapy (research question 3), an added benefit is not proven for these patients.

The assessment concurs with that of the company.

## I 5 Research questions 4a and 4b: patients with mHSPC who are candidates for combination therapy or who are not candidates for combination therapy

### I 5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on relugolix (status: 3 August 2022)
- bibliographical literature search on relugolix (last search on 3 August 2022)
- search in trial registries/trial results databases for studies on relugolix (last search on 24 August 2022)
- search on the G-BA website for relugolix (last search on 3 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on relugolix (last search on 24 October 2022), for search strategies, see I Appendix A of the full dossier assessment

For the benefit assessment, the company identified the HERO study for all research questions (see Section I 3.1.1).

The company stated that no relevant data from the HERO study were available for the assessment of the added benefit of relugolix for patients with mHSPC who are candidates for combination therapy (research question 4a) or who are not candidates for combination therapy (research question 4b). Due to the good general condition of the patients in the HERO study, the company assigned all patients with mHSPC to research question 4a. According to the company, the ACT for these patients was not implemented in the HERO study (monotherapy with leuprorelin). The company presented the results as supplementary information in its dossier.

The assessment of the company is appropriate. Due to the good general condition (ECOG PS of 0 or 1) and the exclusion of patients with relevant comorbidities (such as cardiovascular events), the patients with mHSPC in the HERO study are assumed to be generally candidates for combination therapy. With leuprorelin as monotherapy, the ACT for these patients was not implemented in the HERO study.

### I 5.2 Results on added benefit

The company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with mHSPC who are candidates for combination therapy

(research question 4a) or who are not candidates for combination therapy (research question 4b). For patients with mHSPC, this results in no hint of added benefit of relugolix in comparison with the ACT for research question 4a or research question 4b of the present benefit assessment; an added benefit is therefore not proven.

### I 5.3 Probability and extent of added benefit

Since the company did not provide any data for the assessment of the added benefit of relugolix in comparison with the ACT in patients with mHSPC who are candidates for combination therapy (research question 4a) or who are not candidates for combination therapy (research question 4b), an added benefit is not proven for these patients.

The assessment concurs with that of the company.

## I 6 Probability and extent of added benefit – summary

Table 18 summarizes the result of the assessment of the added benefit of relugolix in comparison with the ACT.

Table 18: Relugolix – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| Patients with advanced hormone-sensitive prostate cancer[b] | | | |
| 1 | Patients who are candidates for local therapy | ▪ radical prostatectomy, if necessary in combination with lymphadenectomy<br>or<br>▪ percutaneous radiotherapy in combination with conventional androgen deprivation[c] or bicalutamide<br>or<br>▪ percutaneous radiotherapy in combination with HDR brachytherapy (only for patients in clinical category cT3) | Added benefit not proven |
| 2 | Patients who are not candidates for local therapy | ▪ conventional androgen deprivation[c]<br>or<br>▪ bicalutamide | Added benefit not proven[d] |
| 3 | Patients with PSA recurrence or clinical recurrence after primary local therapy | Individualized treatment[e] selected from<br>▪ salvage prostatectomy,<br>▪ percutaneous salvage radiotherapy, and<br>▪ percutaneous salvage radiotherapy in combination with conventional androgen deprivationc or bicalutamide;<br>taking into account the prior therapy and the risk of progression | Added benefit not proven |
| Patients with metastatic hormone-sensitive prostate cancer (mHSPC)[f, g] | | | |
| 4a | Patients who are candidates for combination therapy | ▪ conventional androgen deprivation[c] in combination with apalutamide<br>or<br>▪ conventional androgen deprivation[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer)<br>or<br>▪ conventional androgen deprivation[c] in combination with docetaxel with or without prednisone or prednisolone<br>or<br>▪ conventional androgen deprivation[c] in combination with enzalutamide | Added benefit not proven |

Table 18: Relugolix – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| 4b | Patients who are not candidates for combination therapy | ▪ conventional androgen deprivation[c] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that there is no distant metastasis (M0). According to the G-BA, it is assumed that, when determining the ACT, the individual therapeutic decision in the target population was made against long-term observation. Watchful waiting is therefore not considered to be an ACT in the present case.
c. According to the G-BA, conventional androgen deprivation in the context of the present therapeutic indication means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. The drugs buserelin, leuprorelin, goserelin, triptorelin (GnRH agonists) and degarelix (GnRH antagonist) are considered suitable for the implementation of medical castration in the context of conventional androgen deprivation. In the context of a clinical study, the selection of only one of these drugs (single-comparator study) is considered sufficient.
d. The HERO study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
e. According to the G-BA, for the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision which considers the listed criteria (multi-comparator study).
f. It is assumed that there is distant metastasis (M1).
g. According to the G-BA, corresponding to the generally recognized state of medical knowledge, conventional androgen deprivation alone is only indicated for patients with mHSPC for whom a combination therapy – additional therapy to conventional androgen deprivation – is not an option with regard to any comorbidities and the general condition (research question 4b).

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HDR: high dose rate; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen

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 7 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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