Darolutamide (prostate cancer)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Darolutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

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.

IQWiG employees involved in the dossier assessment

- Anja Reinartz
- Simone Heß
- Anne Hüning
- Florina Kerekes
- Katherine Rascher
- Min Ripoll
- Volker Vervölgyi
- Pamela Wronski

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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
AUC	area under the curve
BPI-SF	Brief Pain Inventory – Short Form
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DRS-E	Disease-Related Symptoms – Emotional
DRS-P	Disease-Related Symptoms – Physical
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
FWB	Function and Well-Being
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)
mHSPC	metastatic hormone-sensitive prostate cancer
NFPSI-17	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17 Item Version
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
TSE	Treatment Side Effects

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 darolutamide (in combination with docetaxel and androgen deprivation therapy [ADT]). 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 27 March 2023.

Research question

The aim of this report is to assess the added benefit of darolutamide in combination with docetaxel and ADT (hereinafter referred to as darolutamide + docetaxel + ADT) in comparison with the appropriate comparator therapy (ACT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

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

Table 2: Research question of the benefit assessment of darolutamide + docetaxel + ADT

Therapeutic indication	**ACT**[a]
Adult men with mHSPC	▪ Conventional ADT[b] in combination with apalutamide[c] or ▪ Conventional ADT[b] in combination with enzalutamide[c] or ▪ Conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer) or ▪ **Conventional ADT[b] in combination with docetaxel[c] with or without prednisone or prednisolone**

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. The present ACT was determined under the assumption that it represents the first-line therapy for the metastatic stage.
b. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists.
c. In the present therapeutic indication, it is assumed that, with regard to possible comorbidities and general health, patients are typically eligible for combination therapy – i.e. treatment in addition to conventional ADT.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer

The company followed the ACT specified by the G-BA by selecting as the ACT conventional ADT in combination with docetaxel with or without prednisone or prednisolone from the treatment options.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Study pool and study design

The study pool for the present benefit assessment consists of the ARASENS study.

The ARASENS study is a randomized, double-blind, parallel-group study comparing darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT. It enrolled adult men with mHSPC and distant metastases. Enrolment was limited to patients in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1. Patients had to have started ADT within 12 weeks prior to study inclusion. ADT was defined as either prior orchiectomy or medical castration using gonadotropin-releasing hormone (GnRH) agonists or antagonists. ADT had to be continued throughout the study.

In the ARASENS study, a total of 1305 patients were randomly assigned in a 1:1 ratio to treatment with darolutamide + docetaxel + ADT (N = 651) or placebo + docetaxel + ADT (N = 654). Stratification factors were the extent of disease at baseline (nonregional lymph node metastases only versus bone metastases with or without lymph node metastases and without visceral metastases versus visceral metastases with or without lymph node metastases or with or without bone metastases) and the concentration of alkaline phosphatase at baseline (< upper limit of normal range versus ≥ upper limit of normal range).

Treatment with darolutamide or docetaxel was carried out in accordance with the respective Summary of Product Characteristics (SPC) for the therapeutic indication in question and until disease progression, unacceptable toxicity, withdrawal of informed consent, or discontinuation of treatment as decided by the physician, death, or noncompliance. After treatment discontinuation, patients were allowed to start subsequent therapy.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were outcomes on morbidity and side effects.

The study is ongoing. The present benefit assessment uses the data cutoff for the primary analysis dated 25 October 2021, which was planned to be implemented after 509 deaths. The safety update of the same data cutoff is taken into account for side effects.

Risk of bias

For the ARASENS study, the risk of bias across outcomes is rated as low.

The risk of bias of the results for the outcome of overall survival is likewise rated as low. The certainty of results for the outcome of discontinuation due to adverse events (AEs) is limited

despite the study's low risk of bias. No suitable analyses are available for the symptoms outcome (Disease-Related Symptoms-Physical [DRS-P] subscale of the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17 Item Version [NFPSI-17]), and no outcomes were surveyed for the health-related quality of life category. Therefore, the risk of bias is not assessed for these outcomes. For all other outcomes surveyed in the ARASENS studies, the risk of bias of results is rated as high due to incomplete observations for potentially informative reasons, with the treatment arms differing in treatment durations.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT. This results in an indication of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel+ ADT.

Morbidity

Symptomatic skeletal events

A statistically significant difference in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT was shown for the outcome of symptomatic skeletal events. This results in a hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Worst pain (Brief Pain Inventory – Short Form [BPI-SF] item 3)

For the outcome of worst pain (BPI-SF item 3), a statistically significant difference was found in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT. However, the extent of the effect for this outcome of the category non-serious/non-severe symptoms / late complications was no more than marginal. This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Pain interference (BPI-SF item 9a–g)

A statistically significant difference in favour of darolutamide + docetaxel + ADT in comparison with placebo + docetaxel + ADT was shown for the outcome of pain interference (BPI-SF items 9a–g). However, the 95% confidence interval (CI) for the standardized mean difference (SMD) was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Symptoms (DRS-P subscale of the NFPSI-17)

No suitable analyses are available for the symptoms outcome (DRS-P subscale of the NFPSI-17). This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Symptoms (Treatment Side Effects [TSE] subscale of the NFPSI-17)

A statistically significant difference in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT was shown for the outcome of symptoms (TSE subscale of NFPSI-17). However, the 95%-CI of the SMD was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Health-related quality of life

The ARASENS study did not survey any outcomes suitable to reflect health-related quality of life. This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

For the outcomes of SAEs and severe AEs (CTCAE ≥ grade 3), no statistically significant difference between treatment groups was found. However, there is an effect modification for the characteristic of extent of disease at baseline. In each case, this results in a hint of lesser harm from darolutamide + docetaxel + ADT for patients with visceral metastases with or without lymph node metastases or with or without bone metastases compared to docetaxel + ADT. For patients with nonregional lymph node metastases only as well as for patients with bone metastases with or without lymph node metastases and no visceral metastases, this results in no hint of greater or lesser harm from darolutamide + docetaxel + ADT compared to docetaxel + ADT; hence, there is no proof of greater or lesser harm for these patient groups.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; greater or lesser harm is therefore not proven.

Specific AEs

Skin and subcutaneous tissue disorders, hypertension (each severe AEs)

For each of the outcomes of skin and subcutaneous tissue disorders and hypertension (each severe AEs), a statistically significant difference was found to the disadvantage of darolutamide + docetaxel + ACT in comparison with docetaxel + ADT. For each of them, this results in a hint of greater harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Bone pain (severe AEs)

A statistically significant difference in favour of darolutamide + docetaxel + ADT was shown for the outcome of bone pain (severe AEs). For each of them, this results in a hint of lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

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 the added benefit of the drug combination of darolutamide + docetaxel + ADT in comparison with the ACT is assessed as follows:

In the overall consideration, mostly favourable and only few unfavourable effects of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT were found. Only for overall survival are the observed effects based on the entire observation period. For morbidity and side effects, however, they are based exclusively on the shortened period (side effects: up to 30 days after discontinuation of study medication; morbidity: up to 1 year after discontinuation of study medication).

As a favourable effect, an indication of major added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT was found for the outcome of overall survival. Moreover, there is 1 hint of another favourable effect in the category of serious/severe symptoms / late complications of minor extent. For serious/severe side effects, both favourable and unfavourable effects were found. However, it is questionable whether the favourable effect regarding the outcome of bone pain (severe AEs) is in fact attributable to the outcome category of side effects or whether it rather reflects the symptoms of disease. A

[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].

clear distinction is not possible on the basis of the available information. However, advantages in the overall rates of SAEs and severe AEs are seen only in patients with visceral metastases with or without lymph node metastases or with or without bone metastases. With regard to the benefits in terms of SAEs and severe AEs, it should be noted that these may be due to a mixture of side effects and symptoms or late complications of the disease. In contrast, there are 2 hints of unfavourable effects of considerable or minor extent in the outcome category of serious/serious side effects. Outcomes on health-related quality of life were not recorded. However, neither this circumstance nor the unfavourable effects in the side effects category are thought to jeopardize the favourable effects.

In summary, for patients with mHSPC, this results in an indication of a major added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Table 3 shows a summary of the probability and extent of added benefit of darolutamide + docetaxel + ADT.

Table 3: Darolutamide + docetaxel + ADT – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with mHSPC	▪ Conventional ADT[b] in combination with apalutamide[c] or ▪ Conventional ADT[b] in combination with enzalutamide[c] or ▪ Conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk mHSPC) or ▪ **Conventional ADT[b] in combination with docetaxel[c] with or without prednisone or prednisolone**	Indication of major added benefit[d]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. The present ACT was determined under the assumption that patients are in first-line therapy for the metastatic stage.
b. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists.
c. In the present therapeutic indication, it is assumed that with regard to possible comorbidities and general health, patients are typically eligible for combination therapy – i.e. treatment in addition to conventional ADT.
d. The ARASENS study included only patients with an ECOG-PS ≤ 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG-PS ≥ 2.

ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer

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

I 2 Research question

The aim of this report is to assess the added benefit of darolutamide + docetaxel + ADT in comparison with the ACT in patients with mHSPC.

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

Table 4: Research question of the benefit assessment of darolutamide + docetaxel + ADT

Therapeutic indication	**ACT**[a]
Adult men with mHSPC	▪ Conventional ADT[b] in combination with apalutamide[c] or ▪ Conventional ADT[b] in combination with enzalutamide[c] or ▪ Conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone[c] (only for patients with newly diagnosed high-risk prostate cancer) or ▪ **Conventional ADT[b] in combination with docetaxel[c] with or without prednisone or prednisolone**
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. The present ACT was determined under the assumption that patients are in first-line therapy for the metastatic stage. b. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists. c. In the present therapeutic indication, it is assumed that, with regard to possible comorbidities and general health, patients are typically eligible for combination therapy – i.e. treatment in addition to conventional ADT. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer	

The company followed the ACT specified by the G-BA, selecting (as the ACT) conventional ADT in combination with docetaxel with or without prednisone or prednisolone from the treatment options.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on darolutamide (status: 6 February 2023)
- bibliographical literature search on darolutamide (last search on 6 February 2023)
- search in trial registries / trial results databases for studies on darolutamide (last search on 6 February 2023)
- search on the G-BA website for darolutamide (last search on 6 February 2023)

To check the completeness of the study pool:

- search in trial registries for studies on darolutamide (last search on 3 April 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

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 (yes/no [citation])
Study 17777 (ARASENS[c])	Yes	Yes	No	Yes [3-5]	Yes [6,7]	Yes [8]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

ADT: androgen deprivation therapy; CSR: clinical study report; RCT: randomized controlled trial

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

I 3.2 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: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARASENS	RCT, double-blind, parallel-group	Adult patients (≥ 18 years) with mHSPC[b] ▪ Start of ADT ≤ 12 weeks prior to randomization ▪ ECOG PS ≤ 1	Darolutamide + docetaxel + ADT (N = 651) Placebo + docetaxel + ADT (N = 654)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, withdrawal of informed consent, physician's decision, death, or noncompliance[c] ▪ Docetaxel: at most 6 cycles ▪ ADT: ND Observation[d]: outcome-specific, at most until death, loss to follow-up, withdrawal of consent, or end of study	Total of 301 study centres in Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Finland, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Sweden, Taiwan, United Kingdom, and United States 11/2016–ongoing Data cutoffs: ▪ 17/06/2019[e] ▪ 25/10/2021[f, g] ▪ 31/01/022[h] ▪ 01/08/2022[i]	Primary: overall survival Secondary: morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Metastatic disease was defined as either malignant lesions on bone scan or measurable lymph nodes above the aortic bifurcation or soft tissue / visceral lesions according to RECIST 1.1. Patients exhibiting only regional lymph node metastases below the aortic bifurcation were excluded.
c. The definition of noncompliance is not clear from the study documents; overall, noncompliance as a reason for discontinuation occurred only rarely in the intervention and comparator arms (2.2% vs. 1.8%).
d. Outcome-specific information is provided in Table 8.
e. Predefined futility analysis (planned to be implemented after 153 deaths).
f. Predefined primary analysis (planned to be implemented after 509 deaths).
g. For this data cutoff, updated data on AEs which occurred up to 25/10/2021 are also available as part of a monitoring process but were entered into the database only after this date (referred to by the company as a safety update).
h. According to information provided by the company, this data cutoff implemented after unblinding was a routine safety update after 60 days conducted for the regulatory authorities.
i. Referred to by the company as a safety database extract and implemented after unblinding.

ADT: androgen deprivation therapy; AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; mHSPC: metastatic hormone-sensitive prostate cancer; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study	Intervention	Comparison
ARASENS	Darolutamide 1200 mg/day (2 tablets of 300 mg twice daily) + Docetaxel 75 mg/m^2 BSA i.v. on Day 1 of a cycle (every 21 days for a maximum of 6 cycles)[b] + ADT[c, d]	Placebo (2 tablets twice daily) + Docetaxel 75 mg/m^2 BSA i.v. on Day 1 of a cycle (every 21 days for a maximum of 6 cycles)[b] + ADT[c, d]
	Dose adjustments ▪ Darolutamide/Placebo: treatment interruption for ≤ 28 days and dose adjustment to 300 mg twice daily in case of toxicity (grade ≥ 3 related to the study medication) were permitted; otherwise, treatment was discontinued. ▪ Docetaxel: Dose adjustment to 60 mg/m^2 BSA was allowed in the event of toxicity; otherwise, treatment was discontinued. If docetaxel was discontinued, continuing the study medication was allowed. ▪ ADT: Switching to a GnRH antagonist was allowed	
	Required prior treatment ▪ ADT[c] for ≤ 12 weeks before randomization **Allowed pretreatment** ▪ Concomitant administration of antiandrogens alongside ADT for at least 4 weeks (discontinuation before randomization) ▪ Local therapy of prostate carcinoma before randomization **Disallowed prior treatment** ▪ GnRH agonists/antagonists > 12 weeks before randomization ▪ Radiotherapy, brachytherapy, or radiopharmaceutical substances < 2 weeks before randomization ▪ Second-generation anti-androgens (e.g. enzalutamide) or any other experimental androgen inhibitors, CYP17 inhibitors (e.g. abiraterone acetate), ketoconazole as an antineoplastic treatment for prostate cancer, chemotherapy, or immunotherapy for prostate cancer **Allowed concomitant treatment** ▪ Palliative radiotherapy or surgical therapy ▪ Bisphosphonates and denosumab ▪ Pain therapy **Disallowed concomitant treatment** ▪ Other chemotherapies or antineoplastic therapies ▪ First-generation and second-generation anti-androgens (e.g. bicalutamide, enzalutamide), a switch to GnRH agonists, CYP17 inhibitors (e.g. abiraterone acetate), ketoconazole as an antineoplastic treatment for prostate carcinoma, immunotherapy, experimental or radiopharmaceutical agents	

a. Start within 6 weeks after the first administration of the study medication (darolutamide or placebo).
b. Dexamethasone as a concomitant treatment before the infusion as per SPC was recommended; the combination with prednisolone or prednisone was allowed at the investigator's discretion.
c. Surgical castration (orchiectomy) or medical castration (GnRH agonists/antagonists).
d. Start of ADT ≤ 12 weeks prior to randomization.

ADT: androgen deprivation therapy; BSA: body surface area; GnRH: gonadotropin-releasing hormone; RCT: randomized controlled trial; SPC: Summary of Product Characteristics

Study design

The ARASENS study is a randomized, double-blind, parallel-group study comparing darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT. It enrolled adult men with mHSPC and distant metastases. Enrolment was limited to patients in good general health corresponding to an ECOG-PS ≤ 1. Patients had to have started ADT within 12 weeks prior to study inclusion. ADT was defined as either prior orchiectomy or medical castration using GnRH agonists or antagonists.

In the ARASENS study, a total of 1305 patients were randomly assigned in a 1:1 ratio to treatment with darolutamide + docetaxel + ADT (N = 651) or placebo + docetaxel + ADT (N = 654). Stratification factors were the extent of disease at baseline (nonregional lymph node metastases only versus bone metastases with or without lymph node metastases and without visceral metastases versus visceral metastases with or without lymph node metastases or with or without bone metastases) and alkaline phosphatase concentration at baseline (< upper limit of normal range versus ≥ upper limit of normal range).

Treatment with darolutamide or docetaxel was carried out as per the respective SPC for the therapeutic indication in question [9,10]. The administration of prednisone or prednisolone in addition to docetaxel was allowed at the investigator's discretion. Patients in both treatment arms had to continue the previously started ADT at the physician's discretion throughout the study. Patients who received a GnRH agonist were recommended to receive treatment in combination with an antiandrogen for at least 4 weeks. The antiandrogen had to be discontinued before randomization. Switching to a GnRH antagonist during the study was allowed, as was palliative radiotherapy or surgery if necessary.

Treatment was carried out until disease progression, unacceptable toxicity, withdrawal of informed consent, or discontinuation of treatment at the physician's decision, death, or non-compliance. After treatment discontinuation, patients were allowed to start a subsequent therapy. The study protocol did not restrict the choice of subsequent therapies. According to the study protocol, unblinding of patients and investigators was not planned for this purpose.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were outcomes on morbidity and side effects.

Information on the therapy line

In accordance with the instructions of the G-BA for determining the ACT, it is assumed that the present therapeutic indication is the first line of therapy in the metastatic stage. However, it is not immediately clear from the study documents whether this prerequisite has been met. Module 5 contains information on systemic antineoplastic prior therapies (including ADT). However, it is not clear from this information whether this information covers only ADT started before randomization or whether it includes potential previous treatment lines. As per

the ARASENS inclusion criteria, however, patients were not allowed to have previously received chemotherapy or therapy with other androgen inhibitors such as apalutamide, enzalutamide, or abiraterone acetate, which are recommended by the guidelines for the treatment of mHSPC [11,12]. The patient characteristics (see Table 9) also show that (a) approximately 86% of the included patients were initially diagnosed in the metastatic stage and (b) among all included patients, a median of 2.3 months elapsed between the initial diagnosis and the first dose of study medication.

Based on the study's selected inclusion and exclusion criteria as well as the patient characteristics, it is therefore safe to assume that ARASENS participants are in the first line of treatment in the metastatic stage.

Data cutoffs

A total of 4 data cutoffs are available for the ARASENS study:

- 1st data cutoff (17 June 2019: futility analysis planned a priori (after about 153 deaths)
- 2nd data cutoff dated 25 October 2021: primary analysis planned a priori (after about 509 deaths)

  For this data cutoff, updated data on AEs which occurred up to 25 October 2021 but were only entered into the database after this date are also available as part of a monitoring process (referred to by the company as a safety update). Presumably, all AEs affected by this were systematically included in the company's analyses.
- 3rd data cutoff from 31 January 2022: routine safety update after 60 days for the regulatory authorities (no data submitted by the company due to temporal proximity to the primary data cutoff)
- 4th data cutoff from 1 August 2022: *post hoc* analyses on AEs after patient unblinding

The primary analysis dated 25 October 2021 was used for the present benefit assessment. The safety update is taken into account for the outcomes in the side effects outcome category. For these, the update represents a more valid evidence base and more completely maps the AEs which occurred up to the primary data cutoff.

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: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ARASENS	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent, or end of study
Morbidity	
Symptomatic skeletal events	Until 1 year after discontinuation of study medication
Worst pain (BPI-SF item 3)	Until 1 year after discontinuation of study medication
Pain interference (BPI-SF item 9a–g)	Until 1 year after discontinuation of study medication
Symptoms (subscales DRS-P and TSE of the NFBISI-17)	Until 1 year after discontinuation of study medication
Health-related quality of life	Outcome not recorded
Side effects	
All outcomes in the side effects category	Up to 30 days after discontinuation of the study medication

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; DRS-P: Disease-Related Symptoms-Physical; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Prostate Symptom Index – 17-item version; RCT: randomized controlled trial; SAE: serious adverse event; TSE: treatment side effects

In the ARASENS study, only overall survival was surveyed until study end. The observation periods for the outcomes from the categories of morbidity and side effects were systematically shortened. The outcomes in the morbidity category were to be observed up to 1 year after discontinuation of the study medication and those for side effects up to 30 days after discontinuation of the study medication. 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.

Characteristics of the study population

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

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study Characteristic Category	Darolutamide + docetaxel + ADT N[a] = 651	Placebo + docetaxel + ADT N[a] = 654
ARASENS		
Age [years], mean (SD)	67 (8)	67 (8)
Family origin, n (%)		
Asian	230 (35)	245 (38)
Black or African American	26 (4)	28 (4)
White	345 (53)	333 (51)
Other	7 (1)	2 (< 1)
Missing	43 (7)	46 (7)
Geographical region, n (%)		
Asia-Pacific	229 (35)	244 (37)
North America	125 (19)	119 (18)
Rest of the world	297 (46)	291 (45)
ECOG-PS, n (%)		
0	466 (72)	462 (71)
1	185 (28)	190 (29)
Missing	0	2 (< 1)
Gleason score at initial diagnosis, n (%)		
< 8	122 (19)	118 (18)
≥ 8	505 (78)	516 (79)
Missing	24 (4)	20 (3)
PSA concentration [µg/mL]		
Mean (SD)	248.5 (714.1)	204.7 (742.5)
Median [min; max]	30.3 [0.0; 9219.0]	24.2 [0.0; 11947.0]
Testosterone concentration [ng/mL], n (%)		
< 0.5	339 (52)	353 (54)
≥ 0.5	309 (48)	296 (45)
Missing	3 (< 1)	5 (< 1)
Extent of disease at baseline (TNM classification from the eCRF), n (%)		
Nonregional lymph node metastases only	23 (4)	16 (2)
Bone metastases with or without lymph node metastases and without visceral metastases	517 (79)	520 (80)
Visceral metastases with or without lymph node metastases or with or without bone metastases	111 (17)	118 (18)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study Characteristic Category	Darolutamide + docetaxel + ADT N[a] = 651	Placebo + docetaxel + ADT N[a] = 654
Prostate cancer stage at initial diagnosis (TNM classification)[b], n (%)		
Stage I	12 (2)	10 (2)
Stage II A	18 (3)	10 (2)
Stage II B	15 (2)	10 (2)
Stage III	36 (6)	38 (6)
Stage IV	563 (87)	580 (89)
Stage IV, M0	5 (< 1)	14 (2)
Stage IV, M1	558 (86)	566 (87)
Missing	7 (1)	6 (< 1)
Time from initial diagnosis of prostate cancer to 1st dose of study medication [months], median [min; max]	2.3 [0.6; 296.6]	2.3 [0.5; 200.4]
Time from initial diagnosis of metastases to 1st dose of study medication [months], median [min; max]	2.0 [0.3; 32.7]	2.1 [0.2; 109.2]
Worst pain at baseline (BPI-SF item 3), n (%)		
0: no pain	258 (40)	274 (42)
1-3: mild pain	237 (36)	223 (34)
4-7: moderate pain	109 (17)	121 (19)
8-10: strong pain	28 (4)	16 (2)
Missing	19 (3)	20 (3)
Treatment discontinuation, n (%)[c]	352 (54)	526 (80)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. The company defines stage IV M0 as a time interval of > 3 months between initial diagnosis and initial diagnosis of metastases and stage IV M1 as a time interval of ≤ 3 months between initial diagnosis and initial diagnosis of metastases.
c. Common reasons for treatment discontinuation in the intervention arm versus control arm were disease progression (20% vs. 42%), radiological progression (13% vs. 20%), discontinuation due to AEs (7% vs. 4%), withdrawal of consent (4% vs. 5%).

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; PSA: prostate-specific antigen; RCT: randomized controlled trial; SD: standard deviation; TNM: tumour lymph node metastases

The demographic and clinical characteristics are largely balanced between the 2 treatment arms.

The mean patient age was about 67 years, and most patients were of White family origin. The majority of patients had a Gleason score ≥ 8 and a good general health (ECOG-PS of 0). For approximately 86% of patients, mHSPC was the initial diagnosis, which was established, at median, 2.3 months before the first dose of study medication. At baseline, the majority of patients had bone metastases with or without lymph node metastases, but no visceral metastases.

The proportion of patients with treatment discontinuation was lower in the intervention arm at 54% than in the comparator arm at 80%. There was no information on the number of patients who had discontinued the study.

Treatment duration and observation period

Table 10 shows participants' median and mean treatment duration as well as the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study **Duration of the study phase** **Outcome category**	**Darolutamide + docetaxel + ADT** **N = 651**	**Placebo + docetaxel + ADT** **N = 654**
ARASENS		
Treatment duration [months]		
For darolutamide/placebo		
Median [Q1; Q3]	41.0 [16.6; 46.2]	16.7 [9.4; 36.9]
Mean (SD)	31.9 (16.8)	22.2 (15.4)

Table 10: Information on the course of the study – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study **Duration of the study phase** **Outcome category**	**Darolutamide + docetaxel + ADT** **N = 651**	**Placebo + docetaxel + ADT** **N = 654**
For docetaxel		
Median [min; max]	3.5 [0.0; 11.5]	3.5 [0.0; 5.6]
Mean (SD)	3.4 (1.0)	3.4 (0.8)
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	43.7 [29.9; 47.5]	42.4 [23.8; 46.4]
Mean (SD)	38.3 (13.4)	35.4 (14.6)
Morbidity		
Symptomatic skeletal events		
Median [Q1; Q3]	39.8 [17.7; 44.4]	23.0 [12.3; 41.4]
Mean (SD)	32.0 (15.8)	25.0 (15.1)
Worst pain (BPI-SF item 3)		
Median [Q1; Q3]	13.4 [5.5; 37.0]	9.2 [5.5; 20.7]
Mean (SD)	19.5 (16.5)	14.8 (13.1)
Pain interference (BPI-SF item 9a–g)		
Median [Q1; Q3]	ND[b]	ND[b]
Mean (SD)	ND[b]	ND[b]
Symptoms (DRS-P, TSE)		
Median [Q1; Q3]	41.0 [19.2; 44.5]	23.7 [13.0; 40.5]
Mean (SD)	32.8 (15.1)	25.2 (14.6)
Health-related quality of life	Outcome not recorded[c]	
Side effects		
Median [Q1; Q3]	41.3 [17.3; 46.3]	17.6 [10.4; 37.8]
Mean (SD)	32.3 (16.4)	22.9 (15.1)

a. The observation period was calculated based on the observed time to event/censoring/ end of study of all patients (deceased and non-deceased).
b. The observation durations for the outcome of worst pain (BPI-SF item 3) cannot be assumed to be transferable to the outcome of pain interference (BPI-SF item 9a-g) because patients were censored by ≥ 2 points for the first worsening of the BPI-SF item 3.
c. No outcome was recorded in this category (see Section I 4.1).

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; DRS-P: Disease-Related Symptoms-Physical; max: maximum; min: minimum; N: number of analysed patients; ND: no data; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Prostate Symptom Index – 17-item version; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; TSE: treatment side effects

The median treatment duration in the intervention arm was 41.0 months, about 2.5 times as long as in the comparator arm (16.7 months). The treatment duration for docetaxel, which

should be administered for a maximum of 6 cycles at 21 days each, is comparable in the 2 treatment arms. The median observation period for overall survival is about 43 months in both treatment arms. For the other outcomes, the observation periods were linked to the end of treatment (see Table 8) and were therefore markedly shorter in the comparator arm than in the intervention arm. Further, in the comparator arm, the observation duration for these outcomes equalled at most about half the observation duration for overall survival.

Subsequent therapies

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

Table 11: Information on subsequent systemic antineoplastic therapies (≥ 2% of patients in ≥ 1 treatment arm) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study Drug	Patients with subsequent therapy[a] n (%)	
	Darolutamide + docetaxel + ADT N = 651	Placebo + docetaxel + ADT N = 654
ARASENS		
Total	219 (34)	395 (60)
Abiraterone, abiraterone acetate	112 (51[b])	232 (59[b])
Enzalutamide	48 (22[b])	136 (34[b])
Cabazitaxel, cabazitaxel acetate	57 (26[b])	89 (23[b])
Docetaxel	46 (21[b])	89 (23[b])
Bicalutamide	32 (15[b])	54 (14[b])
Carboplatin	30 (14[b])	31 (8[b])
Radium-223 dichloride	19 (9[b])	34 (9[b])
Etopaside	18 (8[b])	9 (2[b])
Cisplatin	9 (4[b])	13 (3[b])
Flutamide	8 (4[b])	9 (2[b])
Olaparib	5 (2[b])	9 (2[b])
Sipuleucel-T	4 (2[b])	10 (3[b])
Cyclophosphamide	4 (2[b])	6 (2[b])
Ethinylestradiol	4 (2[b])	5 (1[b])
Atezolizumab	5 (2[b])	3 (< 1[b])
Pembrolizumab	4 (2[b])	4 (1[b])
Paclitaxel, paclitaxel albumin	4 (2[b])	1 (< 1[b])

a. Patients may be counted in more than one subsequent therapy.
b. Institute's calculation; based on the proportion of patients with systemic antineoplastic subsequent therapy.

ADT: androgen deprivation therapy; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

According to the study protocol, the choice of the subsequent therapy was not restricted. A total of 34% of patients in the intervention arm and 60% of patients in the comparator arm received subsequent therapy. The proportions of the employed drugs were largely balanced between the treatment arms. The drugs most frequently used as subsequent therapy were abiraterone or abiraterone acetate (51% versus 59%), enzalutamide (22% versus 34%), cabazitaxel or cabazitaxel acetate (26% versus 23%), and docetaxel (21% versus 23%). However, the lists in the study report do not identify the therapy line in which the respective treatment was administered. Overall, the drugs used largely reflect the recommendations of the guidelines for the treatment of prostate cancer [11,12].

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
ARASENS	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

The company outlined that the ARASENS study enrolled mainly patients from Australia, Brazil, Israel, and Europe. It reported the proportion of patients from Europe (about 36%) and the fact that the majority of participants (about 52%) were of White family origin. According to the company, the median participant age (67 years) is comparable to the mean age of prostate cancer patients at disease onset in Germany as surveyed in 2018 (71 years) [13]. The company therefore assumes the available study results to be transferable to the German health care context.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptomatic skeletal-related events
  - worst pain (measured using the BPI-SF item 3).
  - pain interference (measured using the BPI-SF item 9a–g)
  - symptoms (measured using the Disease-Related Symptoms subscale – Physical [DRS-P] of the National Comprehensive Cancer Network / Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17-item version [NFPSI-17])
  - symptoms (measured using the Treatment Side Effects subscale [TSE] of the NFPSI-17)
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study	Outcomes										
	Overall survival	Symptomatic skeletal events[a]	Worst pain (BPI-SF item 3)	Pain interference (BPI-SF item 9a–g)	Symptoms (DRS-P subscale of the NFPSI-17)	Symptoms (TSE subscale of the NFPSI-17)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Specific AEs[b,c]
ARASENS	Yes	Yes	Yes	Yes	No[d]	Yes	No[e]	Yes	Yes	Yes	Yes

a. Includes external radiotherapy to relieve skeletal symptoms; new symptomatic, pathological bone fractures; occurrence of spinal cord compression; tumour-related orthopaedic surgery.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were taken into account (MedDRA coding): skin and subcutaneous tissue disorders (SOC, severe AEs), bone pain (PT, severe AEs), hypertension (PT, severe AEs).
d. No suitable analyses available (see body of text below for reasons).
e. No outcome in this category was surveyed (see body of text below for justification).

ADT: androgen deprivation therapy; AE: adverse events; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms-Physical; MedDRA: Medical Dictionary for Regulatory Affairs; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Prostate Symptom Index – 17-item version; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TSE: treatment side effects

Note on the NFPSI-17 instrument

The company presented analyses of the NFPSI-17 for the outcome categories of morbidity and health-related quality of life. The NFPSI-17 is an instrument of the Functional Assessment of Chronic Illness [FACIT] questionnaire system and was derived from the Functional Assessment of Cancer Therapy – Prostate (FACT-P), with which it shares 14 items [14,15]. The NFPSI-17 was developed to assess symptoms in patients with advanced prostate cancer and consists of a total of 17 items, each rated on a Likert scale ranging from 0 to 4 [16,17]. Higher values indicate a more pronounced manifestation of the respective concept, with a higher value potentially being favourable or unfavourable, depending on the item.

The first 10 items comprise symptoms of the disease and are summarized in the DRS-P subscale. Item 11 asks about the emotional burden from symptoms and forms its own subscale (Disease-Related Symptoms – Emotional [DRS-E]). Items 12 to 15 ask about side

effects of the treatment and form a separate subscale (TSE). Items 16 and 17 ask about general quality of life and form the FWB (Function and Well-Being) subscale. Subscores can be formed for each of the 4 subscales; in addition, the scoring guidelines provide for the formation of a total score across all 17 items (NFPSI-17 Total). The total score has a range of 0 to 68 points. Higher values correspond to milder symptoms for both the subscores and for the total score. The subscales DRS-P and TSE can be clearly assigned to symptoms. The other 3 items of the DRS-E and FWB subscales are neither suitable to completely represent the complex construct of health-related quality of life, nor can they be specifically assigned to the symptoms. The developers of the NFPSI-17 likewise did not assign the instrument to health-related quality of life [14]. Therefore, only the subscales DRS-P and TSE were used to derive added benefit for the present benefit assessment and assigned to the outcome category morbidity.

The company presents analyses of mean differences for the TSE subscale. For the DRS-P subscale, the company presents prespecified responder analyses for first deterioration by ≥ 3 points (scale range 0 to 40). As explained in the Institute's General Methods [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The response criterion is therefore not suitable for reliably depicting a deterioration noticeable for patients. In Module 5, the company presents the results of continuous analyses of the DRS-P subscale purely descriptively. For this outcome, data on mean differences are not available in the company's dossier. Overall, no analyses suitable for deriving added benefit are available concerning the outcome of symptoms (DRS-P subscale of the NFPSI-17).

As no other instruments were used in the ARASENS study to assess health-related quality of life, no data on this outcome category are available for the present benefit assessment.

Note on the surveying of pain

The company's Module 4 A presents 2 operationalizations for the outcome of pain. These include the combined outcome of pain progression as well as worst pain (BPI-SF item 3) presented as supplementary information by the company. The combined outcome of pain progression is made up of the components of confirmed worsening of worst pain (BPI-SF item 3) and initiation of short-acting or long-acting opioid therapy.

Deterioration of worst pain is operationalized as a worsening by ≥ 2 points from baseline, with confirmation at intervals of ≥ 4 weeks at 2 consecutive survey time points. For symptomatic patients (BPI-SF item 3 equalling > 0 at baseline), a minimum score of 4 points after deterioration was defined. The initiation of opioid therapy was operationalized as the start of

pain therapy with opioids. The survey is conducted at baseline and then every 12 weeks up to a maximum of 1 year after discontinuation of the study medication.

The combined outcome of pain progression is not used in the present benefit assessment. This is explained below:

- Firstly, various patients were excluded from the analysis. As per operationalization, symptomatic patients with a BPI-SF item 3 score of 1 at baseline who experience a deterioration by 2 points are excluded from the analyses. In addition, patients who were already taking opioids within 4 weeks prior to randomization were censored on the day of randomization. It is therefore impossible to draw any conclusions on pain progression for these patients. According to Module 5, a total of 42% of patients received an analgesic within 4 weeks prior to randomization. The data fail to show how many of these patients received an opioid.
- Further, in the present operationalization, the worsening of pain measures a confirmed worsening. Since the observation of the outcome is linked to the duration of treatment (see Table 8), confirmation of the deterioration is less likely to be achieved due to the significantly shorter duration of treatment in the comparator arm (see Table 10).

In Module 5, the company also presents prespecified analyses on the outcomes of pain interference (surveyed using BPI-SF item 9a-g) and pain intensity (surveyed using BPI-SF item 3-6). The present benefit assessment employs the outcomes of worst pain (surveyed using BPI-SF item 3; responder analysis including all patients with a worsening by ≥ 2 points) and pain interference (surveyed using BPI-SF item 9a-g). Due to different observation durations in the treatment arms, the operationalization of first deterioration is taken into account for BPI-SF item 3. To derive added benefit, the analysis presented is based on the time-adjusted area under the curve (AUC) for the BPI-SF item 9a-g.

Notes on side effects

For the total rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the company's Module 4 A presents both analyses on all AEs and analyses excluding disease-related events. It defines the following PTs as disease-related events: tumour pain, cancer pain, prostate carcinoma, metastases in the central nervous system, lung metastases, tumour compression, and radical prostatectomy. The company concedes that these events were defined only for patients who did not have an additional primary malignancy. It is unclear whether this procedure completely excludes events which can be attributed to the progression of the underlying disease. Other AEs which occurred in the study, e.g. spinal cord compression, various fractures, or individual PTs from the SOC of diseases of the kidneys and urinary tract, are difficult to differentiate from events related to the underlying disease. Since it cannot be conclusively determined which AE events are actually attributable to the progression of the

underlying disease, the benefit assessment uses the analyses including disease-related events. When interpreting the results, it must be noted that these may be due to a mixture of side effects and symptoms or late complications of the disease.

I 4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study		Outcomes										
	Study level	Overall survival	Symptomatic skeletal events[a]	Worst pain (BPI-SF item 3)	Pain interference (BPI-SF item 9a–g)	Symptoms (DRS-P subscale of the NFPSI-17)	Symptoms (TSE subscale of the NFPSI-17)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Specific AEs[b,c]
ARASENS	L	L	H[d]	H[d]	H[d]	-[e]	H[d]	-[f]	H[d]	H[d]	L[g]	H[d]

a. Includes external radiotherapy to relieve skeletal symptoms; new symptomatic, pathological bone fractures; occurrence of spinal cord compression; tumour-related orthopaedic surgery.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were taken into account (MedDRA coding): skin and subcutaneous tissue disorders (SOC, severe AEs), bone pain (PT, severe AEs), hypertension (PT, severe AEs).
d. Incomplete observations for potentially informative reasons in the presence of between-group differences in observation periods.
e. No suitable analyses available; (see Section I 4.1).
f. No outcome recorded in this category (see Section I 4.1).
g. Despite the low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be restricted (see Section I 4.2).

ADT: androgen deprivation therapy; AE: adverse events; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms-Physical; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Affairs; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Prostate Symptom Index – 17-item version; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TSE: treatment side effects

The risk of bias of the results for the outcome of overall survival is rated as low in the ARASENS study.

For the outcome of discontinuation due to AEs, the certainty of results is reduced, despite a low risk of bias at the study level. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

No suitable analyses are available for the symptoms outcome (DRS-P subscale of the NFPSI-17), and no outcomes were collected for the health-related quality of life category. Therefore, the risk of bias is not assessed for these outcomes.

For all other outcomes surveyed in the ARASENS studies, the risk of bias of results is rated as high due to incomplete observations for potentially informative reasons, with the treatment arms differing in treatment durations.

I 4.3 Results

Table 15 and Table 16 summarize the results on the comparison of darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT in patients with mHSPC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

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

Table 15: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study Outcome category Outcome	Darolutamide + docetaxel + ADT		Placebo + docetaxel + ADT		Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
ARASENS					
Mortality					
Overall survival	651	NR 229 (35.2)	654	48.9 [44.4; NC] 304 (46.5)	0.68 [0.57; 0.80]; < 0.001[a]
Morbidity					
Symptomatic skeletal events	651	NR 95 (14.6)	654	NR 108 (16.5)	0.71 [0.54; 0.94]; 0.016[a]
External radiotherapy to relieve skeletal symptoms	651	NR 60 (9.2)	654	NR 89 (13.6)	-[b]
New symptomatic pathologic bone fracture	651	NR 17 (2.6)	654	NR 8 (1.2)	-[b]
Occurrence of spinal cord compression	651	NR 14 (2.2)	654	NR 9 (1.4)	-[b]
Tumour-related orthopaedic surgery intervention	651	NR 4 (0.6)	654	NR 2 (0.3)	-[b]
Worst pain (BPI-SF item 3)[c]	651	16.6 [13.8; 22.1] 377 (57.9)	654	13.6 [11.0; 16.6] 379 (58.0)	0.85 [0.73; 0.98]; 0.022[a]
Side effects[d]					
AEs (supplementary information)	652	0.5 [0.5; 0.6] 649 (99.5)	650	0.5 [0.4; 0.6] 643 (98.9)	–
SAEs	652	45.6 [34.9; NC] 293 (44.9)	650	40.0 [28.8; NC] 275 (42.3)	0.94 [0.80; 1.11]; 0.464[e]
Severe AEs[f]	652	4.0 [3.1; 6.3] 460 (70.6)	650	3.9 [2.9; 5.7] 439 (67.5)	0.98 [0.86, 1.11]; 0.699[e]
Discontinuation due to AEs[g]	652	NR 124 (19.0)	650	NR 114 (17.5)	0.96 [0.74, 1.24]; 0.759[e]
Skin and subcutaneous tissue disorders (SOC, severe AEs[f])	652	NR 20 (3.1)	650	NR 4 (0.6)	4.64 [1.58; 13.62]; 0.002
Bone pain (PT, severe AEs[f])	652	NR 8 (1.2)	650	NR 19 (2.9)	0.35 [0.15; 0.80]; 0.009
Hypertension (PT, severe AEs[f])	652	NR 43 (6.6)	650	NR 20 (3.1)	1.81 [1.06; 3.09]; 0.027

Table 15: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study Outcome category Outcome	Darolutamide + docetaxel + ADT		Placebo + docetaxel + ADT		Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value

a. Effect and CI: Cox proportional hazards model; p-value: log-rank test. Each stratified by the extent of disease at baseline (only non-regional lymph node metastases versus bone metastases with or without lymph node metastases and without visceral metastases versus visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP value (< ULN versus ≥ ULN).
b. Since only the first event within the composite outcome of symptomatic skeletal events was recorded, an effect estimation for the individual components of the outcome is not meaningfully interpretable.
c. Time to first deterioration. A score increase by ≥ 2 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 10).
d. Results in the side effects category are based on the safety update and also include events defined by the company as disease-related (see also Section I 4.1).
e. Effect and CI: unstratified Cox model; p-value: log-rank test.
f. Operationalized as CTCAE grade ≥ 3.
g. AEs which led to discontinuation of darolutamide/placebo or docetaxel.

ADT: androgen deprivation therapy; AE: adverse event; ALP: alkaline phosphatase; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event; TNM: tumour lymph nodes metastases; ULN: upper limit of normal

Table 16: Results (morbidity, continuous) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study Outcome category Outcome	Darolutamide + docetaxel + ADT			Placebo + docetaxel + ADT			Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT
	N[a]	Value at baseline mean (SD)	Change over the course of the study LS mean [b] [95%-CI]	N[a]	Value at baseline mean (SD)	Change over the course of the study LS mean [b] [95%-CI]	MD [95% CI]; p-value
ARASENS							
Morbidity							
Pain interference (BPI-SF item 9a–g)[c]	618	1.5 (2.0)	1.6 [1.4; 1.8]	617	1.4 (1.9)	1.8 [1.6; 1.9]	−0.15 [−0.30; 0.00]; 0.044 SMD −0.11 [−0.22; 0.00][d]
Pain intensity (BPI-SF items 3-6)[c] (supplementary information)	*618*	*1.5 (1.9)*	*1.6 [1.4; 1.7]*	*617*	*1.4 (1.8)*	*1.7 [1.5; 1.8]*	*−0.08 [−0.22; 0.05]; 0.231* *SMD* *−0.07 [−0.18; 0.05][d]*
	N[a]	**Value at baseline mean (SD)**	**Mean change over the course of the study (SD)[e]**	**N[a]**	**Value at baseline mean (SD)**	**Mean change over the course of the study (SD)[e]**	**MD [95% CI]; p-value**
Symptoms (DRS-P subscale of the NFPSI-17)	No suitable analyses[f]						
Symptoms (TSE subscale of the NFPSI-17)[g]	621	11.6 (2.0)	−0.6 (0.1)	616	11.7 (2.1)	−0.8 (0.1)	0.18 [0.00; 0.36]; 0.044[h] SMD 0.11 [0.00; 0.23]
Health-related quality of life							
Outcome not recorded[i]							

Table 16: Results (morbidity, continuous) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Study Outcome category Outcome	Darolutamide + docetaxel + ADT			Placebo + docetaxel + ADT			Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT
	N[a]	Value at baseline mean (SD)	Change over the course of the study LS mean [b] [95%-CI]	N[a]	Value at baseline mean (SD)	Change over the course of the study LS mean [b] [95%-CI]	MD [95% CI]; p-value

a. Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on other patient numbers.
b. Unless otherwise stated, from the time-adjusted analysis of the AUC of the ITT population; ANCOVA analysis with value at baseline, treatment, extent of disease, and ALP value as covariates.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range for BPR-SF item 9a-g: 0 to 70; for BPI-SF item 3-6: 0-40).
d. Institute's calculation based on MD and CI of the time-adjusted analyses of AUC.
e. From the MMRM analysis.
f. No suitable analyses available; for the reasoning, see Section I 4.1 of the present dossier assessment.
g. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0-16).
h. MMRM with unstructured variance matrix, value at baseline as a continuous covariate, treatment, time in the form of the study day, and the interaction term "treatment × visit". Effect refers to the change from baseline over the course of the study.
i. No outcome recorded in this category (see Section I 4.1).

ADT: androgen deprivation therapy; ANCOVA: analysis of covariance; AUC: area under the curve; BPI-SF: Brief Pain Inventory –- Short Form; CI: confidence interval; DRS-P: Disease-Related Symptoms-Physical; ITT: intention to treat; LS: least squares; MD: mean difference; MMRM: mixed model with repeated measures; N: number of analysed patients; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17-item version; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; TSE: treatment side effects

On the basis of the available information, at most an indication, e.g. of added benefit, can be derived for the outcome of overall survival, and due to the high risk of bias or limited certainty of results (discontinuation due to AEs), at most hints can be derived for the outcome categories of morbidity and side effects.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT. This results in an indication of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Morbidity

Symptomatic skeletal-related events

A statistically significant difference in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT was shown for the outcome of symptomatic skeletal events. This results in a hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Worst pain (BPI-SF item 3)

For the outcome of worst pain (BPI-SF item 3), a statistically significant difference was found in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT. For this outcome of the non-serious/non-severe symptoms / late complications category, however, the extent of the effect was no more than marginal (see Section I 5.1). This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Pain interference (BPI-SF item 9a–g)

A statistically significant difference in favour of darolutamide + docetaxel + ADT in comparison with placebo + docetaxel + ADT was shown for the outcome of pain interference (BPI-SF items 9a–g). However, the 95% confidence interval (CI) for the standardized mean difference (SMD) was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Symptoms (DRS-P subscale of the NFPSI-17)

No suitable analyses are available for the symptoms outcome (DRS-P subscale of the NFPSI-17) (for reasoning, see Section I 4.1). This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Symptoms (TSE subscale of the NFPSI-17)

A statistically significant difference in favour of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT was shown for the outcome of symptoms (TSE subscale of NFPSI-17). However, the 95%-CI of the SMD was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Health-related quality of life

In the ARASENS study, no outcome suitable to reflect health-related quality of life was recorded (for justification, see Section I 4.1). This results in no hint of an added benefit of

darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3)

For the outcomes of SAEs and severe AEs (CTCAE ≥ grade 3), no statistically significant difference between treatment groups was found. However, there is an effect modification for the characteristic of extent of disease at baseline (see Section I 4.4). In each case, this results in a hint of lesser harm from darolutamide + docetaxel + ADT for patients with visceral metastases with or without lymph node metastases or with or without bone metastases compared to docetaxel + ADT. For patients with nonregional lymph node metastases only as well as for patients with bone metastases with or without lymph node metastases and no visceral metastases, this results in no hint of greater or lesser harm from darolutamide + docetaxel + ADT compared to docetaxel + ADT; hence, there is no proof of greater or lesser harm for these patient groups.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; greater or lesser harm is therefore not proven.

Specific AEs

Skin and subcutaneous tissue disorders, hypertension (each severe AEs)

For each of the outcomes of skin and subcutaneous tissue disorders and hypertension (each severe AEs), a statistically significant difference was found to the disadvantage of darolutamide + docetaxel + ACT in comparison with docetaxel + ADT. For each of them, this results in a hint of greater harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Bone pain (severe AEs)

A statistically significant difference in favour of darolutamide + docetaxel + ADT was shown for the outcome of bone pain (severe AEs). For each of them, this results in a hint of lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (< 65 years versus 65 to 74 years versus ≥ 75 years)
- extent of disease at baseline (nonregional lymph node metastases only versus bone metastases with or without lymph node metastases and without visceral metastases versus visceral metastases with or without lymph node metastases or with or without bone metastases)

Interaction tests are conducted 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 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

The results are presented in Table 17.

Table 17: Subgroups (side effects) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

Study Outcome Characteristic Subgroup	Darolutamide + docetaxel + ADT N	Darolutamide + docetaxel + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + docetaxel + ADT N	Placebo + docetaxel + ADT Median time to event in months [95% CI] Patients with event n (%)	Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT HR [95% CI][a]	 p-value[b]
ARASENS						
SAEs[c]						
Extent of disease						
Nonregional lymph node metastases only	23	ND 14 (60.9)	15	ND 8 (53.3)	1.30 [0.54; 3.13]	0.551
Bone metastases with or without lymph node metastases and without visceral metastases	518	ND 234 (45.2)	518	ND 205 (39.6)	1.04 [0.86; 1.25]	0.706
Visceral metastases with or without lymph node metastases or with or without bone metastases	111	ND 45 (40.5)	117	ND 62 (53.0)	0.58 [0.39; 0.85]	0.005
Total					Interaction[d]:	0.048
Severe AEs[e]						
Extent of disease						
Nonregional lymph node metastases only	23	ND 21 (91.3)	15	ND 11 (73.3)	1.79 [0.85; 3.77]	0.120
Bone metastases with or without lymph node metastases and without visceral metastases	518	ND 369 (71.2)	518	ND 345 (66.6)	1.01 [0.88; 1.18]	0.851
Visceral metastases with or without lymph node metastases or with or without bone metastases	111	ND 70 (63.1)	117	ND 83 (70.9)	0.71 [0.52; 0.98]	0.035
Total					Interaction[c]:	0.039

a. Unstratified Cox model with treatment, subgroup, and interaction between treatment and subgroup as covariates.
b. Log-rank test.
c. Results in the side effects category are based on the safety update and also include events which were defined as disease-related by the company (see also Section I 4.1).
d. Interaction term from Cox model.
e. Operationalized as CTCAE grade ≥ 3.

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; PSA: prostate-specific antigen; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Side effects

SAEs, severe AEs

There was an effect modification for the characteristic of extent of disease at baseline for the outcomes of SAEs and severe AEs.

No statistically significant difference between treatment groups was shown for patients exhibiting only nonregional bone metastases. This results in no hint of greater or lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; greater or lesser harm is therefore not proven for this patient group.

For patients with bone metastases with or without lymph node metastases and no visceral metastases, there was no statistically significant difference between the treatment groups. This results in no hint of greater or lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; greater or lesser harm is therefore not proven for this patient group.

For patients with visceral metastases with or without lymph node metastases or with or without bone metastases, there was a statistically significant difference in favour of darolutamide + docetaxel + ADT. For this patient group, this results in a hint of lesser harm from darolutamide + docetaxel + ADT in comparison with docetaxel + ADT in each case.

With regard to benefits in terms of SAEs and severe AEs, it should be noted that these may be due to a mixture of side effects and symptoms or late complications of the disease.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [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 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 18).

Determination of the outcome category for the outcomes on morbidity

For the morbidity outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptomatic skeletal events

The outcome of symptomatic skeletal events is deemed to be serious/severe. Said outcome is a composite outcome consisting of the components of external radiotherapy to relieve skeletal symptoms, new symptomatic, pathological bone fractures, occurrence of spinal cord compression, and tumour-related orthopaedic surgical intervention for bone metastasis. These events represent a burden on patients and their daily activities. Overall, the outcome is to be deemed severe or serious.

Pain (BPI-SF item 3), pain interference (BPI-SF items 9a–g)

At baseline, the score for worst pain (BPI-SF item 3) was 0 in about 41% of patients and 1 to 3 in about 35% of patients (see Table 9), which corresponds to no pain or mild pain. The company did not present any information on participants' scores after pain progression. For the outcome of pain interference (BPI-SF items 9a-g), patients had a low mean score at baseline (1.5 points; see Table 16), with hardly any changes being observed in the course of the study. Overall, the 2 outcomes of most severe pain (BPI-SF item 3) and pain interference (BPI-SF items 9a–g) were therefore assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Table 18: Extent of added benefit at outcome level: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NR vs. 48.9 HR: 0.68 [0.57; 0.80] p < 0.001 Probability: indication	Outcome category: mortality CI_u < 0.85 Added benefit; extent: major
Outcomes with shortened observation period		
Morbidity		
Symptomatic skeletal events	NR vs. NR HR: 0.71 [0.54; 0.94] p = 0.016 Probability: hint	Outcome category: serious/severe symptoms / late complications 0.90 ≤ CI_u < 1.00 Added benefit; extent: minor
Worst pain (BPI-SF item 3)	16.6 vs. 13.6 HR: 0.85 [0.73; 0.98] p = 0.022	Outcome category: non-serious/non-severe symptoms / late complications 0.90 ≤ CI_u < 1.00 Lesser/Added benefit not proven[c]
Pain interference (BPI-SF item 9a–g)	Adjusted values: 1.6 vs. 1.8 MD: -0.15 [-0.30; 0.00] p = 0.044 SMD: -0.11 [-0.22; 0.00][d, e]	Lesser/Added benefit not proven
Symptoms (DRS-P subscale of the NFPSI-17)	No suitable analyses[f]	Lesser/Added benefit not proven
Symptoms (TSE subscale of the NFPSI-17)	Adjusted change: -0.6 vs. -0.8 MD: 0.18 [0.00; 0.36] p = 0.044 SMD: 0.11 [0.00; 0.23][e]	Lesser/Added benefit not proven
Health-related quality of life		
	Outcome not recorded[g]	

Table 18: Extent of added benefit at outcome level: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs Extent of disease		
Nonregional lymph node metastases only	ND[h] HR: 1.30 [0.54; 3.13] p = 0.551	Greater/Lesser harm not proven
Bone metastases with or without lymph node metastases and without visceral metastases	ND[h] HR: 1.04 [0.86; 1.25] p = 0.706	Greater/Lesser harm not proven
Visceral metastases with or without lymph node metastases or with or without bone metastases	ND[h] HR: 0.58 [0.39; 0.85] p = 0.005 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable
Severe AEs Extent of disease		
Only non-regional lymph node metastases	ND[h] HR: 1.79 [0.85; 3.77] p = 0.120	Greater/lesser harm not proven
Bone metastases with or without lymph node metastases and without visceral metastases	ND[h] HR: 1.01 [0.88; 1.18] p = 0.851	Greater/Lesser harm not proven
Visceral metastases with or without lymph node metastases or with or without bone metastases	ND[h] HR: 0.71 [0.52; 0.98] p = 0.035 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.0$ Lesser harm; extent: minor
Discontinuation due to AEs	NR vs. NR HR: 0.96 [0.74; 1.24] p = 0.759	Greater/Lesser harm not proven
Skin and subcutaneous tissue disorders (severe AEs)	NR vs. NR HR: 4.64 [1.58; 13.62] HR: 0.22 [0.07; 0.63][i] p = 0.002 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% Greater harm; extent: considerable

Table 18: Extent of added benefit at outcome level: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Bone pain (severe AEs)	NR vs. NR HR: 0.35 [0.15; 0.80] p = 0.009 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable
Hypertension (severe AEs)	NR vs. NR HR: 1.81 [1.06; 3.09] HR: 0.55 [0.32; 0.94][i] p = 0.027 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. Institute's calculation.
e. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f. No suitable analyses available; for the reasoning, see Section I 4.1 of the present dossier assessment.
g. No outcome recorded in this category (see Section I 4.1).
h. No data on the median time to event is available for the safety update.
i. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CI_U: upper limit of the confidence interval; CI_L: lower limit of the confidence interval; DRS-P: Disease-Related Symptoms-Physical; HR: hazard ratio; MD: mean difference; ND: no data; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index - 17-item version; NR: not reached; SAE: serious adverse event; SMD: standardized mean difference; TSE: treatment side effects

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects from the assessment of darolutamide + docetaxel + ADT compared with docetaxel + ADT

Favourable effects	**Unfavourable effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: indication of added benefit – extent: major	–
Outcomes with shortened observation period	
Serious/severe symptoms / late complications ▪ Symptomatic skeletal events: hint of an added benefit – extent: minor	–
Serious/severe side effects ▪ SAEs: ▫ extent of the disease (visceral metastases with or without lymph node metastases or with or without bone metastases): hint of lesser harm – extent: considerable ▪ Severe AEs: ▫ extent of the disease (visceral metastases with or without lymph node metastases or with or without bone metastases): hint of lesser harm – extent: minor ▪ Bone pain (severe AEs): hint of lesser harm – extent: considerable	Serious/severe side effects ▪ Skin and subcutaneous tissue disorders (severe AEs): hint of greater harm – extent: considerable ▪ Hypertension (severe AEs): hint of greater harm – extent: minor
No outcomes were recorded on health-related quality of life.	
ADT: androgen deprivation therapy; AE: adverse event; SAE: serious adverse event	

In the overall consideration, mostly favourable and only few unfavourable effects of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT were found. Only for overall survival are the observed effects based on the entire observation period. For morbidity and side effects, however, they are based exclusively on the shortened period (side effects: up to 30 days after discontinuation of study medication; morbidity: up to 1 year after discontinuation of study medication).

As a favourable effect, an indication of major added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT was found for the outcome of overall survival. Moreover, there is 1 hint of another favourable effect in the category of serious/severe symptoms / late complications of minor extent. For serious/severe side effects, both favourable and unfavourable effects were found. However, it is questionable whether the favourable effect regarding the outcome of bone pain (severe AEs) is in fact attributable to the outcome category of side effects or whether it rather reflects the symptoms of disease. A clear distinction is not possible on the basis of the available information. Advantages regarding the overall rates of SAEs and severe AEs are seen only in patients with visceral metastases with or without lymph node metastases or with or without bone metastases. With regard to benefits in terms of SAEs and severe AEs, it should be noted that these may be due to a mixture

of side effects and symptoms or late complications of the disease. In contrast, there are 2 hints of unfavourable effects of considerable or minor extent in the outcome category of serious/serious side effects. Outcomes on health-related quality of life were not recorded. However, neither this circumstance nor the unfavourable effects in the side effects category are thought to jeopardize the favourable effects.

In summary, for patients with mHSPC, this results in an indication of a major added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT.

Table 20 summarizes the result of the assessment of added benefit of darolutamide + docetaxel + ADT in comparison with the ACT.

Table 20: Darolutamide + docetaxel + ADT – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with mHSPC	▪ Conventional ADT[b] in combination with apalutamide[c] or ▪ Conventional ADT[b] in combination with enzalutamide[c] or ▪ Conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk mHSPC) or ▪ **Conventional ADT[b] in combination with docetaxel[c] with or without prednisone or prednisolone**	Indication of major added benefit[d]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. The present ACT was determined under the assumption that patients are in first-line therapy for the metastatic stage.
b. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.
c. In the present therapeutic indication, it is assumed that, with regard to possible comorbidities and general health, patients are typically eligible for combination therapy – i.e. treatment in addition to conventional ADT.
d. The ARASENS study included only patients with an ECOG-PS ≤ 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG-PS of ≥ 2.

ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer

The assessment described above concurs with the company's assessment.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

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