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Darolutamide (prostate cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Darolutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2020). 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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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25
EQ-5D	European Quality of Life-5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
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)
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
MMRM	mixed-effects model repeated measures
nmCRPC	non-metastatic castration-resistant prostate cancer
PSA	prostate-specific antigen
PSADT	PSA doubling time
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SMQ	Standardized MedDRA Query
SPC	Summary of Product Characteristics
SOC	System Organ Class
VAS	visual analogue scale

2 Benefit assessment

2.1 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. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 30 April 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report was the assessment of the added benefit of darolutamide in comparison with watchful waiting while maintaining ongoing conventional androgen deprivation therapy (ADT) as appropriate comparator therapy (ACT) in adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of darolutamide

Therapeutic indication	**ACT[a]**
Adult men with non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease	Watchful waiting while maintaining ongoing conventional ADT[b]
a. Presentation of the respective ACT specified by the G-BA. b. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone	

The company followed the G-BA's specification on the ACT.

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

Results

The study ARAMIS was included in the benefit assessment.

Study design and data cut-offs

The ARAMIS study is a randomized, double-blind study comparing darolutamide in combination with ADT versus treatment with ADT and the additional administration of placebo. It included adult men with high-risk nmCRPC. The included patients either had to have undergone bilateral orchiectomy before randomization, or continue medical ADT using gonadotropin-releasing hormone (GnRH) agonists or antagonists in addition to the study medication.

A total of 1509 patients were randomized to the 2 study arms (darolutamide + ADT: N = 955; placebo + ADT: N = 554). Treatment with darolutamide + ADT is in compliance with the specifications of the Summary of Product Characteristics (SPC).

Double-blind treatment in the study was conducted until the time point of confirmed metastasis or unacceptable toxicity. After the double-blind phase, patients from the darolutamide + ADT arm had the option to continue treatment with darolutamide + ADT unblinded, and patients from the placebo + ADT arm could switch to unblinded treatment with darolutamide + ADT. The primarily planned analysis of the study was conducted with the first data cut-off at the end of the double-blind phase.

Primary outcome of the study is metastasis-free survival (MFS); patient-relevant secondary outcomes are overall survival and outcomes on morbidity, health-related quality of life and adverse events (AEs).

The ARAMIS study is still ongoing. Results on the following data cut-offs are available for the assessment:

- first data cut-off (3 September 2018): planned primary analysis after occurrence of 385 events in the primary outcome “MFS”
- second data cut-off (15 November 2019): planned final analysis for all outcomes after occurrence of 240 deaths

For the present benefit assessment, the first data cut-off is used for all outcomes except for the outcome “all-cause mortality”. This is justified by the fact that the follow-up observation in the ARAMIS study is systematically shortened for all outcomes, except for the outcome “overall survival”, partly for several reasons. According to the planning of the study, the follow-up observation depends on various factors, i.e. whether the patients discontinue therapy before developing metastatic disease and receive subsequent therapy that is prohibited according to the planning of the study, whether they were treated with placebo + ADT during the blinded phase, and whether the patients receive darolutamide + ADT in the unblinded phase.

Since systematic follow-up observation of all patients is only conducted for the outcome “overall survival”, the present benefit assessment used both data cut-offs in the overall

assessment for this outcome. For all other outcomes, the results from the second data cut-off are not usable for the present benefit assessment due to the unsystematic follow-up observation.

There are additional factors for the results of the second data cut-off: Not for all included outcomes are analyses available for the second data cut-off; the study was unblinded after the first data cut-off, and there is a high proportion of patients with subsequent treatment switch from placebo + ADT to darolutamide + ADT (it remains unclear how the high proportion of patients who switched treatment affected the results of the second data cut-off); a large proportion of patients had already discontinued therapy at the first data cut-off, with a large difference between the study arms; there are no corresponding figures for the second data cut-off.

Risk of bias

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

The risk of bias of the results for the outcome "overall survival" was rated as low for the first data cut-off. There was a high risk of bias for the results of the second data cut-off due to the high proportion of patients who switched to unblinded treatment with darolutamide + ADT after the double-blind treatment phase with placebo. In the present data situation, however, it can rather be assumed that the treatment effect is underestimated at the second data cut-off after the treatment switching from the comparator therapy to the intervention (see below). Overall, there is therefore a high certainty of results for the outcome "overall survival".

For all other outcomes, except for the outcome "discontinuation due to AEs", the risk of bias of the results was rated as high.

Mortality

Overall survival

On the basis of the event time analyses both at the first and at the second data cut-off, there was a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT for the outcome "overall survival". The estimated treatment effect at the second data cut-off was of a comparable magnitude. In the present situation, it can rather be assumed that the estimated treatment effect in the second data cut-off after treatment switching from placebo + ADT to darolutamide + ADT is underestimated. Overall, a high certainty of results is assumed for the outcome. In the overall consideration, this resulted in an indication of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "overall survival" in the present data situation.

Morbidity

Symptomatic skeletal-related events

The outcome "symptomatic skeletal-related events" is a composite outcome. Analyses on the individual components are not available.

On the basis of the event time analyses, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "symptomatic skeletal-related events". Due to the high risk of bias and the missing analyses on the individual components, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT.

Prostate cancer-related invasive procedures

On the basis of the event time analyses, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "prostate cancer-related invasive procedures". Due to the high risk of bias, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT.

Pain progression (Brief Pain Inventory-Short Form [BPI-SF] Item 3 or initiation of opioid treatment

On the basis of the event time analyses, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "pain progression" (BPI-SF Item 3 or initiation of opioid treatment). Due to the high risk of bias, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "pain progression".

Pain interference (BPI-SF Items 9a–g)

On the basis of the mean differences, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "pain interference" (BPI-SF Items 9a–g). There is no information on the standardized mean difference (SMD) in the form of Hedges' g; calculations by the Institute cannot be conducted due to missing values. Thus, an estimation of the relevance of the effect is not possible. This resulted in no hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "pain interference".

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

On the basis of the mean differences, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "health status" (EQ-5D VAS). The SMD in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "health status" (EQ-5D VAS). In contrast to the analyses on the other outcomes (except health-related quality of life), the analyses refer to a markedly shorter observation period (16 weeks).

Health-related quality of life

Functional Assessment of Cancer Therapy-Prostate (FACT-P)

On the basis of the responder analyses, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "health-related quality of life" (deterioration in the FACT-P total score). Due to the high risk of bias, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for this outcome. In contrast to the analyses on the other outcomes (except the outcome "health status"), the analyses refer to a markedly shorter observation period (16 weeks).

Side effects

Serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs

On the basis of the event time analyses, no statistically significant differences between the treatment groups were shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from darolutamide + ADT in comparison with watchful waiting + ADT for these outcomes; greater or lesser harm is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug darolutamide in comparison with the ACT are assessed as follows:

In the overall consideration, there are exclusively positive effects of darolutamide + ADT in comparison with watchful waiting + ADT for adult men with nmCRPC who are at high risk of developing metastatic disease. An indication of a considerable added benefit was shown for the outcome "overall survival". In addition, there were hints of an added benefit with the extent "considerable" or "major" both for serious/severe symptoms/late complications and for non-serious/non-severe symptoms/late complications. A hint of an added benefit of minor extent was shown for health-related quality of life.

[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].

In summary, there is an indication of considerable added benefit of darolutamide in comparison with the ACT "watchful waiting while maintaining ongoing conventional ADT" for men with nmCRPC who are at high risk of developing metastatic disease.

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

Table 3: Darolutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease[b]	Watchful waiting while maintaining ongoing conventional ADT[c]	Indication of considerable added benefit

a. Presentation of the respective ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the ARAMIS study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
c. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone

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

2.2 Research question

The aim of the present report was the assessment of the added benefit of darolutamide in comparison with watchful waiting while maintaining ongoing conventional ADT as ACT in adult men with nmCRPC who are at high risk of developing metastatic disease.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of darolutamide

Therapeutic indication	**ACT[a]**
Adult men with non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease	Watchful waiting while maintaining ongoing conventional ADT[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 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: 2 March 2020)
- bibliographical literature search on darolutamide (last search on 24 February 2020)
- search in trial registries/trial results databases for studies on darolutamide (last search on 21 February 2020)
- search on the G-BA website for darolutamide (last search on 21 February 2020)

To check the completeness of the study pool:

- search in trial registries for studies on darolutamide (last search on 7 May 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: darolutamide + ADT vs. watchful waiting + 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])
ARAMIS	Yes	Yes	No	No[c]	Yes [3-7]	Yes [8,9]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

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

2.3.2 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 + ADT vs. placebo + ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARAMIS	RCT, double-blind, parallel	Adult patients with non-metastatic castration-resistant[b] prostate cancer who are at high risk of developing metastatic disease (PSADT ≤ 10 months[c])	Darolutamide + ADT (N = 955) placebo + ADT (N = 554)	Screening: up to 28 days Double-blind treatment: until the time point of confirmed metastasis or unacceptable toxicity[d] Observation[e]: outcome-specific, at most until death or end of study	409 study centres in 36 countries worldwide[f] 9/2014–ongoing First data cut-off: 3 Sep 2018 (primary analysis) Second data cut-off: 15 Nov 2019	Primary: metastasis-free survival Secondary: outcomes of the categories of mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Defined as rising PSA levels at 3 time points at least 1 week apart during continuous ADT administration (in case of pretreatment with of antiandrogens, the most recent PSA value must be obtained ≥ 4 weeks after completion of that treatment); in addition, serum testosterone had to be at castrate level on GnRH agonist or antagonist therapy or after bilateral castration (< 1.7 nmol/L [50 ng/dL]).
c. In addition, patients had to have a PSA level of ≥ 2 ng/mL at screening.
d. Following the double-blind treatment phase (after 385 events in the primary outcome), patients from both study arms can optionally receive unblinded treatment with darolutamide until the end of the study (planned for 30 June 2021).
e. Outcome-specific information is provided in Table 8.
f. Argentina, Australia, Austria, Belarus, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Finland, France, Germany, Great Britain, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Peru, Poland, Portugal, Romania, Russia, Serbia, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, USA

ADT: androgen deprivation therapy; AE: adverse event; GnRH: gonadotropin-releasing hormone; N: number of randomized patients; PSA: prostate-specific antigen; PSADT: PSA doubling time; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
ARAMIS	Darolutamide 600 mg twice daily, orally + ADT[a]	Placebo, twice daily, orally + ADT[a]
	Prior and concomitant treatment not allowed: ▪ second-generation anti-androgens (e.g. enzalutamide) ▪ CYP17 inhibitors (e.g. abiraterone acetate) ▪ oral ketoconazole[b] ▪ oestrogens or 5-alpha reductase inhibitors (e.g. finasteride)[c] ▪ first-generation anti-androgens (e.g. bicalutamide)[d] ▪ chemotherapy or immunotherapy for prostate cancer[e] ▪ longterm use of systemic corticosteroids > 10 mg prednisone equivalent/day[c] ▪ radiotherapy[f] ▪ treatment with bone-preserving substances (e.g. denosumab) to prevent skeletal-related events[f] ▪ major surgery[c] **Concomitant treatment** not recommended: ▪ moderate and strong CYP3A4 inducers (e.g. rifampicin)[g] allowed: ▪ short-term use of systemic corticosteroids > 10 mg prednisone equivalent/day for up to 28 days ▪ treatment with bone-preserving substances (e.g. denosumab) for the therapy of osteoporosis on a stable dose	

a. Surgical castration or continuous treatment with GnRH agonists or antagonists during the study; testosterone at castrate level (< 1.7 nmol/L [50 ng/dL]).
b. Pretreatment with a duration of less than 28 days allowed.
c. Not allowed within 28 days before randomization and during treatment with the study medication.
d. Not allowed within at least 28 days before screening and during treatment with the study medication.
e. Exception: adjuvant/neoadjuvant treatment completed more than 2 years before randomization.
f. Not allowed within 12 weeks before randomization and during treatment with the study medication.
g. Protocol Amendment 4 of 6 July 2019 removed the recommendation to avoid moderate CYP3A4 inducers.

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

Study design

The ARAMIS study is a randomized, double-blind study comparing darolutamide in combination with ADT versus treatment with ADT and the additional administration of placebo.

The study included adult men with high-risk nmCRPC. The presence of high-risk prostate cancer was defined by a prostate-specific antigen (PSA) doubling time (PSADT) of ≤ 10 months. In addition, patients had to have a PSA level of ≥ 2 ng/mL at screening. Patients

with a history of metastatic disease at any time point or presence of detectable metastases by blinded central reading within 42 days before start of the study treatment were excluded from the study. Presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation at study inclusion was allowed, however. Patients with symptomatic locoregional symptoms requiring medical intervention (e.g. moderate or severe urinary obstruction or hydronephrosis due to prostate cancer) were excluded. Patients had to have a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The included patients either had to have undergone bilateral orchiectomy before randomization, or continue medical ADT using GnRH agonists or antagonists in addition to the study medication. In case of medical castration, the testosterone level had to be below 50 ng/dL.

A total of 1509 patients were enrolled and, stratified according to treatment with bone-sparing substances at baseline (yes/no) and PSADT (≤ 6 months/> 6 months), randomized in a ratio of 2:1 to the 2 study arms of darolutamide + ADT (N = 955) and placebo + ADT (N = 554).

Treatment with darolutamide + ADT is in compliance with the specifications of the SPC [10].

Double-blind treatment in the study was conducted until the time point of confirmed metastasis or unacceptable toxicity. After the double-blind phase, patients under the study medication had the option to continue treatment with darolutamide + ADT unblinded, and patients from the placebo + ADT arm could switch to unblinded treatment with darolutamide + ADT. Patients who did not choose unblinded treatment with darolutamide + ADT had their end-of-study visit at the time point of unblinding and then received follow-up observation according to the planning of the study (see Table 8). The primarily planned analysis of the study was conducted with the first data cut-off at the end of the double-blind phase.

Primary outcome of the study is MFS; patient-relevant secondary outcomes are overall survival and outcomes on morbidity, health-related quality of life and AEs.

Data cut-offs

The ARAMIS study is still ongoing. Results on the following data cut-offs are available for the assessment:

- First data cut-off (3 September 2018):

  The planned primary analysis was to be conducted for all outcomes after occurrence of 385 events in the primary outcome "MFS". The data cut-off was actually carried out after 437 MFS events, however. According to the company, based on the review of the U.S. Food and Drug Administration (FDA), the deviation was due to a delay in the confirmation of Protocol Amendment 3 of 26 February 2018 [11]. In this amendment, the case number calculation was adjusted based on results of studies on enzalutamide and apalutamide. Due to the new calculation, the number of events in the primary outcome for

the first data cut-off was reduced from 572 to 385. This had no consequence for the present benefit assessment.

- Second data cut-off (15 November 2019):

  The analysis at the second data cut-off was planned as final analysis for all outcomes after occurrence of 240 deaths

In accordance with the planning of the study, no further analyses until the end of the study (planned: 30 June 2021) are defined.

For the present benefit assessment, the first data cut-off is used for all outcomes included. Results on the basis of the second data cut-off are usable only for the outcome "overall survival" so that both data cut-offs are considered for this outcome and interpreted in the overall consideration. There are several problems for analyses on the basis of the second data cut-off:

- In accordance with the planning, the follow-up observation in the ARAMIS study is systematically shortened for all outcomes, except for the outcome "overall survival", partly for several reasons. One reason that leads to the systematic shortening of the observation period for all outcomes is that the observation is only planned up to the last administration of the study medication if the patients stop treatment with the study medication before confirmed metastasis and receive subsequent therapy that is prohibited according to the planning of the study (see Table 8). For the first data cut-off, this applied to 4.4% of the patients in the intervention arm and 16.2% of the patients in the comparator arm (see Table 10). There is no corresponding information for the second data cut-off. Therefore, the influence of this unsystematic follow-up observation on the results for the second data cut-off cannot be assessed.
- For some of the included outcomes, there are additional reasons leading to unsystematic follow-up observation after the end of the double-blind treatment. For example, according to the planning of the study, the follow-up observation additionally depends on whether the patients were treated with placebo + ADT during the blinded phase, or receive darolutamide + ADT in the unblinded phase. It remains unclear for both data cut-offs how many patients were affected by this unsystematic follow-up observation.

A more detailed description of the planned and actual follow-up observation in the study can be found further below in the present section under "Treatment duration and follow-up observation" and "Follow-up observation".

There are additional factors for the results at the second data cut-off:

- For the second data cut-off, analyses are not available for all included outcomes.
- The study was unblinded after the first data cut-off, and there is a high proportion of patients with subsequent treatment switching from placebo + ADT to darolutamide + ADT (30.7% of the total number of patients randomized to the placebo + ADT arm, see

Table 9). It remains unclear how the high proportion of patients with treatment switching affected the results at the second data cut-off.

- A large proportion of patients had discontinued treatment already at the first data cut-off, with a large difference between the study arms (35.5% in the darolutamide + ADT arm versus 63.9% in the placebo + ADT arm, see Table 9). There is no information on the proportion of patients with treatment discontinuation for the second data cut-off.

The approach in the present benefit assessment not to use the results based on the second data cut-off, with the exception of the outcome "overall survival", concurs with the approach of the company, which also used the first data cut-off for the derivation of the added benefit. The company also presented results of the second data cut-off, however. The approach to consider both data cut-offs for the derivation of the added benefit for the outcome "all-cause mortality" concurs with the approach of the company.

Operationalization and implementation of the ACT

The G-BA specified "watchful waiting while maintaining ongoing conventional ADT" as ACT. For the present benefit assessment, watchful waiting was operationalized as a follow-up strategy that particularly comprises diagnosis of disease progression. According to the current S3 guideline [12], imaging should not be routinely performed during follow-up care, and the patient should not be subjected to unnecessary examinations. Application of imaging techniques should be indicated precisely together with a specific research question and only when therapeutic consequences can be expected. For instance, indications for imaging include changes of the clinical state (symptom increase, change of general condition) that might require further therapies.

In the ARAMIS study, regular visits take place at 16-week intervals for the patients of both treatment arms. Among other things, the patients undergo radiographic examination with regard to metastases using computed tomography and bone scan during these visits. The S3 guideline does not foresee such regular radiographic examinations, however, given the 16-week rhythm, the examinations take place at rather long intervals. In case of suspected disease progression, radiographic examinations can be performed at an earlier point in time. In addition, further examinations are carried out regularly, for some outcomes and patients even beyond the end of therapy, for example on the development of symptomatic skeletal events or pain progression.

Overall, the diagnostic approach in the ARAMIS study was regarded as appropriate despite the deviation from the S3 guideline described above, and, in connection with the continued administration of ADT in the study, the ACT (watchful waiting while maintaining ongoing conventional ADT) was considered adequately implemented.

Treatment duration and 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 + ADT vs. placebo + ADT (multipage table)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ARAMIS	
Mortality	
Overall survival	Until death or end of study
Morbidity	
Symptomatic skeletal-related events	Until death or end of study[a]
Prostate cancer-related invasive procedures	Until death or end of study[a]
Pain progression (BPI-SF Item 3 or initiation of opioid treatment)	Until death or end of study[a]
Pain interference (BPI-SF Items 9 a–g)	Until death or end of study[a]
Health status (EQ-5D VAS)	▪ For patients of the darolutamide + ADT arm who continued darolutamide + ADT in the unblinded treatment phase: ▫ until 28 days (+ 7 days) after the last dose of the study medication in the unblinded phase ▪ For all other patients[a]: ▫ no follow-up observation planned (last recording at the end of the double-blind treatment phase)
Health-related quality of life	
FACT-P[b]	▪ For patients of the darolutamide + ADT arm who continued darolutamide + ADT in the unblinded treatment phase: ▫ until 28 days (+ 7 days) after the last dose of the study medication in the unblinded phase ▪ For all other patients[a]: ▫ no follow-up observation planned (last recording at the end of the double-blind treatment phase)
Side effects	
All outcomes in the category of side effects	▪ For patients who receive darolutamide + ADT in the unblinded treatment phase[c]: ▫ until 28 days (+ 7 days) after the last dose of the study medication in the unblinded phase ▪ For all other patients[a]: ▫ no systematic follow-up observation planned (last recording of all AEs at the end of the double-blind treatment phase)[d]

a. There is no follow-up observation for patients with subsequent therapy that is prohibited according to the planning of the study before confirmed metastasis.
b. Follow-up observation of the prostate cancer-specific subscale was conducted until death or end of study if patients receive no subsequent therapy that is prohibited according to the planning of the study before confirmed metastasis.
c. This also includes patients who were treated with placebo + ADT in the double-blind treatment phase and then switched to unblinded treatment with darolutamide + ADT.
d. After the end-of-treatment visit, only AEs are recorded that are considered to be associated with the study medication or the study procedures.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT (multipage table)

Study Outcome category Outcome	Planned follow-up observation
ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

In the ARAMIS study, only the outcome "overall survival" is observed until death or end of study for all patients. The observation periods for all other included outcomes are systematically shortened, partly for several reasons.

For all outcomes, except for the outcome "overall survival", patients have no follow-up observation if they discontinue treatment with the study medication before confirmed metastasis and receive subsequent therapy prohibited according to the planning of the study (including, for example, immunotherapy, cytotoxic chemotherapy, and other systemic antineoplastic therapy).

In addition, patients are observed only until the end of the double-blind treatment for the outcomes "health status" (recorded using the EQ-5D VAS) and "health-related quality of life" (recorded using the FACT-P), with the exception of the prostate cancer-specific subscale. Patients from the intervention arm who receive subsequent unblinded treatment with darolutamide + ADT are continued to be observed also afterwards, but only for another 28 days after the last dose of unblinded darolutamide + ADT. Patients who switch from placebo + ADT to unblinded treatment with darolutamide + ADT are exempt from the follow-up observation after the double-blind treatment phase.

For outcomes of the category of side effects, systematic observation of all patients is also only conducted until the end of the double-blind treatment. Patients who then switch either from the intervention or the control arm to unblinded treatment with darolutamide + ADT are continued to be observed (but also only until 28 days after the last dose of unblinded darolutamide + ADT). All patients who do not receive unblinded treatment with darolutamide + ADT after the double-blind treatment are exempt from systematic follow-up observation. This leads to selective recording of events that are considered to be associated with the study medication or study procedures.

The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" are therefore systematically shortened. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes for all patients over the total period of time, as is the case 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 – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT (multipage table)

Study Characteristics Category	Darolutamide + ADT N = 955	Placebo + ADT N = 554
ARAMIS		
Age [years], mean (SD)	74 (8)	73 (8)
Gleason score at diagnosis, n (%)		
< 7	217 (22.7)	142 (25.6)
≥ 7	711 (74.5)	395 (71.3)
Unknown	27 (2.8)	17 (3.1)
Disease duration: time between first diagnosis and randomization [years], median [min; max]	7.2 [0.0; 28.0]	7.0 [0.0; 29.0]
PSA doubling time, n (%)		
≤ 6 months	667 (69.8)	371 (67.0)
> 6 months	288 (30.2)	183 (33.0)
ECOG PS, n (%)		
0	650 (68.1)	391 (70.6)
1	305 (31.9)	163 (29.4)
Regional lymph node classification at baseline (N classification), n (%)		
N0	524 (54.9)	286 (51.6)
N1	87 (9.1)	62 (11.2)
NX	319 (33.4)	193 (34.8)
Unknown	25 (2.6)	13 (2.3)
Number of prior hormonal therapies, n (%)		
1	177 (18.5)	103 (18.6)
≥ 2	727 (76.1)	420 (75.8)
Unknown	51 (5.3)	31 (5.6)
Therapy with bone-sparing substances at baseline, n (%)		
Yes	36 (3.8)	28 (5.1)
No	919 (96.2)	526 (94.9)
Initial therapy of prostate cancer, n (%)		
Chemical castration	403 (42.2)	252 (45.4)
Prostatectomy	239 (25.0)	134 (24.2)
Radiotherapy	177 (18.5)	89 (16.1)
Orchiectomy	91 (9.5)	50 (9.0)
Active surveillance	12 (1.3)	7 (1.3)
Other	32 (3.4)	22 (4.0)

Table 9: Characteristics of the study population – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT (multipage table)

Study Characteristics Category	Darolutamide + ADT N = 955	Placebo + ADT N = 554
Region, n (%)		
Europe	621 (65.0)	346 (62.5)
North America	108 (11.3)	76 (13.7)
Asia-Pacific	119 (12.5)	67 (12.1)
Rest of the world	107 (11.2)	65 (11.7)
Treatment discontinuation until first data cut-off[a], n (%)	339 (35.5)	354 (63.9)
Treatment switch after completion of double-blind treatment phase, n (%)	-	170 (30.7)
Study discontinuation, n (%)	ND	ND

a. ND at the second data cut-off.

ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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; vs.: versus

The demographic and clinical characteristics are largely balanced between the 2 study arms. The mean age of the patients is 74 years, and about 64% of the patients are from Europe. The median time of the diagnosis of prostate cancer was about 7 years prior to randomization. About 10% of the patients had lymph node involvement at baseline. Only a small proportion of the patients (about 9%) had androgen deprivation by previous orchiectomy. The majority of the patients (about 75%) had received ≥ 2 previous hormonal therapies before the start of the study.

There is a high proportion of patients with treatment discontinuation in the study, with a markedly higher number of patients who had discontinued treatment in the placebo + ADT arm than in the darolutamide + ADT arm at the first data cut-off (about 28 percentage points difference between the study arms). In addition, the majority of patients who were still receiving placebo + ADT as their study medication at the time of the first data cut-off switched to unblinded treatment with darolutamide + ADT (170 of 200 patients; a total of 30.7% of the patients randomized to the placebo + ADT arm). There is no information on the proportions of patients with treatment discontinuation for the second data cut-off. There is no information on the proportion of patients with study discontinuation.

Table 10 summarizes further data on patients with treatment discontinuation until the first data cut-off.

Table 10: Information on patients with treatment discontinuation until the first data cut-off (3 September 2018) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study Characteristics Category	Darolutamide + ADT N = 955	Placebo + ADT N = 554
ARAMIS		
Treatment discontinuation total, n (%)	339 (35.5)	354 (63.9)
Adverse event	86 (9.0)	47 (8.5)
Confirmed metastasis[a]	112 (11.7)	129 (23.3)
Judgment of investigator	54 (5.7)	91 (16.4)
Personal reasons	68 (7.1)	78 (14.1)
Protocol violation	13 (1.4)	7 (1.3)
Other reasons	6 (0.6)	2 (0.4)
Patients with treatment discontinuation without metastases total, n (%)	188 (19.7)	175 (31.6)
Increased PSA level, n (%)	88 (9.2)	136 (24.5)
Prohibited subsequent therapy before metastasis, n (%)	42 (4.4)[b]	90 (16.2)[b]

a. Discrepancy in comparison with patients with metastasis recorded in the primary outcome of the study: darolutamide + ADT: 188 (18.8%) and placebo + ADT: 197 (35.6%). The FDA review [11] cites the following possible reasons for the discrepancy: metastasis (≥ 1 week) after treatment discontinuation for other reasons, continued treatment after metastasis (≥ 1 week) and subsequent treatment discontinuation for other reasons, censoring in the analysis of the primary outcome before treatment discontinuation due to metastasis.
b. Institute's calculation.

ADT: androgen deprivation therapy; FDA: U.S. Food and Drug Administration; n: number of patients in the category; N: number of randomized patients; PSA: prostate-specific antigen; RCT: randomized controlled trial; vs. versus

The information on the reasons for treatment discontinuation shows that the high discontinuation rates and differences between the treatment arms can only partly be directly attributed to disease progression, with 11.7% of the patients with confirmed metastasis in the darolutamide + ADT arm and 23.3% in the placebo + ADT arm. In addition to confirmed metastasis, there are also high discontinuation rates and differences between the study arms for treatment discontinuations conducted at the investigator's discretion or for personal reasons.

Since patients and physicians are not blinded to the recording of the PSA levels in the study, the high proportions and higher discontinuation rates in the placebo + ADT arm could be partly due to increased PSA levels, which could lead to conclusions about disease progression by patients or physicians. This cannot be conclusively assessed, as the study does not record elevated PSA levels as a reason for treatment discontinuation. However, data on patients with treatment discontinuation without metastasis at the first data cut-off show that a large proportion of these patients also had elevated PSA levels (9.2% in the darolutamide + ADT arm and 24.5% in the placebo + ADT arm).

The differential rates of treatment discontinuation between the study arms were taken into account in the assessment of the risk of bias (see Section 2.4.2).

Follow-up observation

Table 11 shows the mean and median treatment duration of the patients and the observation period for individual outcomes if available.

Table 11: Information on the course of the study – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study **Duration of the study phase** **Outcome category**	**Darolutamide + ADT** **N = 955**	**Placebo + ADT** **N = 554**	**Darolutamide + ADT** **N = 955**	**Placebo + ADT** **N = 554**
ARAMIS	First data cut-off (3 Sep 2018)		Second data cut-off (15 Nov 2019)	
Treatment duration [months]				
Median [min; max]	14.8 [0; 44.3]	11.0 [0.1; 40.5]	18.5 [0; 48.0][a]	11.6 [0; 45.0][a]
Mean (SD)	16.8 (9.5)	12.3 (8.3)	19.9 (10.5)	13.5 (9.1)
Observation period [months][b]				
Overall survival	ND	ND	ND	ND
Morbidity	ND	ND	ND	ND
Health-related quality of life	ND	ND	ND	ND
Side effects	ND	ND	ND	ND

a. For the second data cut-off, discrepant data on the median treatment duration [months] are available in Module 4 A, cited in Section 4.4 as 25.8 [0; 59] in the darolutamide + ADT arm vs. 11.0 [1; 12] in the placebo + ADT arm.
b. The median overall observation period provided in the publication by Fizazi et al. [8] is 17.9 months at the first data cut-off.

ADT: androgen deprivation therapy; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration for both data cut-offs was notably longer in the intervention arm of the ARAMIS study than in the comparator arm. The difference in the treatment duration between the study arms was presumably mainly due to differences in the treatment discontinuation rates (at the first data cut-off: 35.5% in the darolutamide + ADT arm versus 63.9% in the placebo + ADT arm; no information is available for the second data cut-off).

The median observation period for both study arms together was 17.9 months at the first data cut-off. Separate data on the observation periods for the 2 study arms and data on the observation periods for individual outcomes are not available.

For outcomes with a systematically shortened period of follow-up observation according to the planning of the study (see above), it can be assumed that there are also corresponding differences in the observation period between the study arms due to the differences in treatment duration.

Overall, it remains unclear how many patients were affected by the unsystematic follow-up observation described above. The company did not present any corresponding information in Module 4 A. Information in the FDA review shows how many patients had received subsequent therapy prohibited according to the planning of the study after treatment discontinuation before metastasis at the first data cut-off, and are therefore not receiving any follow-up observation (4.4% of the patients in the intervention arm and 16.2% in the comparator arm, see Table 10). In addition, according to the European Medicines Agency (EMA) assessment report [13], with 18.2% of the patients in the darolutamide + ADT arm and 29.4% in the placebo + ADT arm, high proportions of patients and more patients in the comparator arm had discontinued the follow-up phase of the study until the first data cut-off. Complete follow-up observation of all patients can be assumed for the outcome "overall survival", as, according to the planning of the study, separate enquiries to all patients who were still alive were planned at each data cut-off. For all other outcomes, the actual magnitude of the differences in follow-up observation between the study arms remains unclear overall. This was considered in the assessment of the risk of bias (see Section 2.4.2).

Subsequent therapies

Table 12 shows which subsequent therapies patients received after discontinuing the study medication.

Table 12: Information on subsequent therapies at the first data cut-off (3 September 2018) (cytotoxic chemotherapy or antineoplastic therapy for metastatic prostate cancer) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study Drug	Patients with subsequent therapy n (%)	
	Darolutamide + ADT N = 955	Placebo + ADT N = 554
ARAMIS		
Total, n (%)	100 (10.5)	130 (23.5)
Abiraterone	13 (1.4[a])	23 (4.2[a])
Docetaxel	49 (5.1[a])	66 (11.9[a])
Enzalutamide	18 (1.9[a])	19 (3.4[a])
Other[b]	13 (1.4[a])	16 (2.9[a])

a. Institute's calculation.

b. Including all drugs received by ≥ 2% of the patients with subsequent therapy (bicalutamide, flutamide, carboplatin, cisplatin and estramustine).

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

Regarding the type of subsequent therapy after the end of treatment, there were no restrictions in the ARAMIS study for patients after metastasis. For the study, information on subsequent therapies administered is only available on cytotoxic chemotherapies or antineoplastic therapies that are approved for the treatment of metastatic prostate cancer. In total, 10.5% of the patients in the intervention arm and 23.5% of the patients in the comparator arm were receiving such

therapy at the time of the first data cut-off. The most common subsequent therapies in the study were docetaxel, abiraterone and enzalutamide.

According to information in the EMA assessment report [13], a large proportion of patients continued treatment with the study medication after the initial occurrence of metastases until confirmed metastasis (17.6% in the darolutamide + ADT arm and 33.9% in the placebo + ADT arm), which was not provided for in the planning of the study. The interval period of continued treatment with the study medication was between 1 and 337 days. According to the EMA, the company justified this deviation from the study planning with the fact that queries during the process of centralized confirmation of metastasis and scheduling of appointments to inform the patients of their disease progression had led to delays in some cases.

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

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			
ARAMIS	Yes	Yes	Yes[a]	Yes[a]	Yes	Yes	Low
a. The study was unblinded after the first data cut-off.							
ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the ARAMIS study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company described that 409 study centres in 36 countries/regions in North America, Asia-Pacific, Europe, and the rest of the world had included patients in the ARAMIS study. It reported the proportion of patients from Europe (about 64%) and the fact that the majority of the included patients were Caucasian (about 79%). According to the company, the median age of the included patients (74 years) is comparable to the mean age of prostate cancer patients at disease onset in Germany recorded in 2016 (72 years). According to the company, it can therefore be assumed that the available study results are 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.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - symptomatic skeletal-related events
  - prostate cancer-related invasive procedures
  - pain progression (BPI-SF Item 3 or initiation of opioid treatment
  - pain interference (BPI-SF Items 9a–g)
  - health status (measured using the EQ-5D VAS)
- Health-related quality of life
  - measured using the FACT-P total score
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

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

Table 14 shows for which outcomes data were available in the study included.

Table 14: Matrix of outcomes – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study	Outcomes										
	Overall survival	Symptomatic skeletal-related events	Prostate cancer-related invasive procedures	Pain progression (BPI-SF Item 3 or initiation of opioid treatment)	Pain interference (BPI-SF Items 9a–g)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs (CTCAE grade ≥ 3)[a]	Discontinuation due to AEs	Further specific AEs
ARAMIS (first data cut-off)	Yes[b]	Yes	Yes	Yes	Yes	Yes[c]	Yes[c]	Yes	Yes	Yes	No[d]

a. In addition to AEs occurring under the treatment, AEs that occurred between the signing of the informed consent form and randomization are also included.
b. The second data cut-off from 15 November 2019 is additionally used for the outcome.
c. No usable analyses are available for the first data cut-off; analyses at week 16 are used for the benefit assessment, see Section 2.4.3.
d. No usable analyses are available for the choice of specific AEs; the company did not present analyses on SOCs and PTs in accordance with the required threshold values for all AE categories. In addition, there is insufficient information on the operationalization of AEs of special interest or SMQs prespecified in the study.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

- In Module 4 A, the company presented analyses on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC QLQ-PR25). This questionnaire is recorded every 16 weeks in the course of the ARAMIS study. According to the authors of the EORTC QLQ-PR25, this questionnaire is only valid in conjunction with the core questionnaire (QLQ-C30) [14], which is not recorded in the ARAMIS study.
- For outcomes on side effects except for severe AEs (CTCAE grade ≥ 3), the company did not address the handling of disease-related events for the operationalization used for the present benefit assessment (see Section 2.4.3). In accordance with the planning of the study, events of disease progression should not be recorded per se as SAEs in the ARAMIS study. For signs or symptoms caused by progression, it is not the underlying cause that is recorded as an SAE, but the sign or symptom itself. Information on common AEs shows that, overall, a small proportion of events attributable to disease progression were recorded at the first data section. For severe AEs, the company addressed the

handling of disease-related events for the operationalization presented by the company (see Section 2.4.3). It remains unclear which events it deducted, however. It can be inferred from the available documents that this affected one patient in the placebo + ADT arm.

Overall, it is assumed for the present assessment that the results for the overall rates of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs are not influenced to a relevant degree by disease-related events. The analyses presented by the company for these outcomes were therefore not used for the present benefit assessment.

- Specific AEs:
  - The company did not present any suitable data for the choice of specific AEs on the basis of frequency and differences between the treatment arms for SAEs and severe AEs (CTCAE grade ≥ 3). For SAEs and severe AEs (CTCAE grade ≥ 3), the event time analyses by System Organ Class (SOC) and Preferred Term (PT) presented by the company, refer to events that occurred in at least 5% of the patients in one study arm. However, the required threshold values for these outcomes are events that occurred in at least 10 patients and in at least 1% of the patients in one study arm. Overall, a choice of specific AEs on the basis of the analyses presented by the company was therefore not made. Results of the threshold values presented by the company are presented in Appendix B of the full dossier assessment.
  - In Module 4 A, the company also presented analyses on the prespecified AEs of special interest the recording of which had been prespecified in the ARAMIS study. According to the company, most of these AEs were based on Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs). However, it is not clear from Module 4 A which AEs were concerned. The analyses are therefore not usable for the present benefit assessment.

2.4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study	Outcomes											
	Study level	Overall survival (first data cut-off/second data cut-off)	Symptomatic skeletal-related events	Prostate cancer-related invasive procedures	Pain progression (BPI-SF Item 3 or initiation of opioid treatment)	Pain interference (BPI-SF Items 9a–g)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Further specific AEs
ARAMIS (First data cut-off[a])	L	L/H[b]	H[c]	H[c]	H[d]	H[d, e]	H[f, g]	H[f, g]	H[c]	H[c]	L[h]	–[i]

a. Unless otherwise noted.
b. Treatment switch to a relevant extent (> 30% of the patients in the comparator arm switched to unblinded treatment with the intervention after the end of the double-blind study phase).
c. Incomplete observations for potentially informative reasons; differences in the observation periods between the treatment groups.
d. Increasing proportion of missing values in the course of the study, which also differs markedly between the treatment arms (already less than 70% from week 48).
e. Unclear proportion of patients not included in the analysis.
f. No usable analyses are available for the first data cut-off; analyses at week 16 are used for the benefit assessment, see Section 2.4.3.
g. High proportion of patients not included in the analysis (> 10%).
h. Despite low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".
i. No usable analyses available; for reasons, see Section 2.4.1.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

In the ARAMIS study, the risk of bias of the results for the outcome "overall survival" was rated as low for the first data cut-off. There was a high risk of bias for the results of the second data cut-off due to the high proportion of patients who switched to unblinded treatment with darolutamide + ADT after the double-blind treatment phase with placebo + ADT. In the present data situation, however, it can rather be assumed that the treatment effect is underestimated at the second data cut-off after the treatment switching from the comparator therapy to the intervention. The overall consideration across both data cut-offs therefore resulted in a high certainty of results for the outcome "overall survival". This deviates from the assessment of the company insofar as the company did not provide any information on the risk of bias for the second data cut-off.

For all other outcomes, except for the outcome "discontinuation due to AEs", the risk of bias of the results at the first data cut-off was rated as high. This was due to incomplete observations for potentially informative reasons, differences in the observation periods between the treatment groups or high or unclear proportions of missing values. This deviates from the assessment of the company, which rated the risk of bias of the results at the first data cut-off as low for all outcomes.

The certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias.

2.4.3 Results

Table 16, Table 17 and Table 18 summarize the results on the comparison of darolutamide + ADT with placebo + ADT in patients with nmCRPC who are at high risk of developing metastatic disease. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the presented event time analyses are found in Appendix A of the full dossier assessment.

Table 16: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT (multipage table)

Study Outcome category Outcome Time point	Darolutamide + ADT N	Darolutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Darolutamide + ADT vs. placebo + ADT HR[a] [95% CI]; p-value[b]
ARAMIS					
Mortality					
Overall survival					
First data cut-off[c]	955	NA [44.4; NC] 78 (8.2)	554	NA 58 (10.5)	0.71 [0.50; 0.99]; 0.045
Second data cut-off[d]	955	NA [56.1; NC] 148 (15.5)	554	NA [46.9; NC] 106 (19.1)	0.69 [0.53; 0.88]; 0.003
Morbidity					
Symptomatic skeletal-related events[c]	955	NA 16 (1.7)	554	NA 18 (3.2)	0.43 [0.22; 0.84]; 0.011
External radiotherapy to relieve skeletal symptoms				ND	
New symptomatic pathologic bone fracture				ND	
Spinal cord compression				ND	
Tumour-related orthopaedic-surgical intervention				ND	
Prostate cancer-related invasive procedures[c]	955	NA 34 (3.6)	554	NA 44 (7.9)	0.39 [0.25; 0.61]; < 0.001
Pain progression (BPI-SF Item 3[e] or initiation of opioid treatment)[c]	955	40.3 [33.2; 41.2] 251 (26.3)	554	25.4 [19.1; 29.6] 178 (32.1)	0.65 [0.53; 0.79]; < 0.001
Pain progression (BPI-SF Item 3[e]) (supplementary information)[c]	*955*	*NA [40.3; NC] 238 (24.9)*	*554*	*26.9 [22.1; 31.4] 168 (30.3)*	*0.66 [0.54; 0.81]; < 0.001*
Side effects					
AEs (supplementary information)[c]	954	3.9 [3.2; 4.2] 794 (83.2)	554	4.3 [3.8; 4.6] 426 (76.9)	–
SAEs[c]	954	44.4 [44.4; NC] 237 (24.8)	554	NA 111 (20.0)	1.14 [0.91; 1.43]; 0.263[f]
Severe AEs (CTCAE grade ≥ 3)[c, g]	954	38.5 [34.1; NC] 280 (29.4)	554	NA 137 (24.7)	1.11 [0.91; 1.36]; 0.311[f]
Discontinuation due to AEs[c]	954	NA 86 (9.0)	554	NA 48 (8.7)	0.95 [0.67; 1.36]; 0.791[f]

Table 16: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT (multipage table)

Study Outcome category Outcome Time point	Darolutamide + ADT N	Darolutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Darolutamide + ADT vs. placebo + ADT HR[a] [95% CI]; p-value[b]
a. Unless stated otherwise: effect and confidence interval: Cox proportional hazards model stratified by PSA doubling time ≤ 6 months vs. > 6 months and therapy with bone-sparing substances at randomization: yes vs. no. b. Unless stated otherwise: p-value: log-rank test stratified by the factors PSA doubling time ≤ 6 months vs. > 6 months and therapy with bone-sparing substances at randomization: yes vs. no. c. First data cut-off from 3 September 2018. d: Second data cut-off from 15 November 2019. e. Time to first deterioration by ≥ 2 points from baseline. f. p-value: Cox proportional hazards model stratified by PSA doubling time ≤ 6 months vs. > 6 months and therapy with bone-sparing substances at randomization: yes vs. no. g. In addition to AEs occurring under the treatment, AEs that occurred between the signing of the informed consent form and randomization are also included. ADT: androgen deprivation therapy; AE: adverse event; 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 one) event; N: number of analysed patients; NA not achieved; NC: not calculable; ND: no data; PSA: prostate-specific antigen; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus					

Table 17: Results (morbidity, continuous) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study Outcome category Outcome	Darolutamide + ADT			Placebo + ADT			Darolutamide + ADT vs. placebo + ADT
	N[a]	Values at baseline mean (SD)	Change at first data cut-off[b] Mean[c] [95% CI]	N[a]	Values at baseline mean (SD)	Change at first data cut-off[b] Mean[c] [95% CI]	MD [95% CI]; p-value
ARAMIS							
Morbidity							
Pain interference (BPI-SF Items 9a–g)[d]	ND	ND	1.1 [1.0; 1.3]	ND	ND	1.3 [1.2; 1.4]	−0.2 [−0.3; −0.1]; ND Hedges' g: –[e]
Pain intensity (BPI-SF Items 3–6)[d] (supplementary information)	*ND*	*ND*	*1.3 [1.1; 1.4]*	*ND*	*ND*	*1.4 [1.3; 1.6]*	*−0.2 [−0.3; −0.1]; ND* *Hedges' g: –[e]*
Health status (EQ-5D VAS)[f]	868	70.3 (21.4)	Values at week 16 mean (SD): 74.9 (17.3)	489	71.5 (17.0)	Values at week 16 mean (SD) 72.7 (18.3)	2.2 [0.2; 4.2]; 0.028[f] Hedges' g: 0.12 [0.01; 0.24]

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. 3 September 2018.
c. Unless stated otherwise, LSM analysis (time-adjusted AUC) of the ITT population.
d. A positive change from baseline to the first data cut-off indicates deterioration; a negative effect estimation indicates an advantage for the intervention.
e. Calculation by the Institute not possible due to missing data; due to the rather small differences of the mean values, no relevant effect can be assumed
f. Institute's calculation of MD and Hedges' g based on the data at week 16.

ADT: androgen deprivation therapy; AUC: area under the curve; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; LSM: least squares mean; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 18: Results (health-related quality of life, dichotomous) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

Study Outcome category Outcome	Darolutamide + ADT		Placebo + ADT		Darolutamide + ADT vs. placebo + ADT
	N[a]	Patients with event at week 16 n (%)	N[a]	Patients with event at week 16 n (%)	RR [95% CI]; p-value[b]
ARAMIS					
Health-related quality of life					
FACT-P					
Total score – deterioration[c] by ≥ 10 points	848	167 (19.7)	478	117 (24.5)	0.80 [0.65; 0.99]; 0.041
Physical wellbeing – deterioration[c] by ≥ 3 points	863	138 (16.0)	483	101 (20.9)	0.76 [0.61; 0.96]
Social/family wellbeing – deterioration[c] by ≥ 3 points	862	193 (22.4)	484	133 (27.5)	0.81 [0.67; 0.99]
Emotional wellbeing – deterioration[c] by ≥ 3 points	857	142 (16.6)	484	108 (22.3)	0.74 [0.59; 0.93]
Functional wellbeing – deterioration[c] by ≥ 3 points	857	183 (21.4)	483	126 (26.1)	0.82 [0.67; 1.00]
Prostate cancer-specific subscale – deterioration[c] by ≥ 3 points				ND[d]	

a. Patients who received a questionnaire.
b. p-value: unadjusted chi-square test.
c. Deterioration means decrease in score.
d. The company did not present the analyses on patients with event at week 16 for this subscale. Event time analyses on the deterioration by ≥ 3 points from baseline are available for the first data cut-off (3 September 2018). The median time [95% CI] to event in months was: 11.1 [11.0; 11.1] for darolutamide + ADT vs. 7.9 [7.5; 11.1] for placebo + ADT in 590 (61.8) vs. 354 (63.9%) patients with event, with HR [95% CI]: 0.80 [0.70; 0.91].

ADT: androgen deprivation therapy; CI: confidence interval; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

On the basis of the available data, at most indications can be derived for the outcome "overall survival" in the present data situation. Due to the high risk of bias or due to limited certainty of results (discontinuation due to AEs), at most hints, e.g. of an added benefit, can be determined for all other outcomes.

Mortality

Overall survival

On the basis of the event time analyses both at the time point of the first and at the time point of the second data cut-off, there was a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT for the outcome "overall survival". The estimated treatment effect at the second data cut-off was of a comparable magnitude, but

more precise. In the present situation, it can rather be assumed that the estimated treatment effect at the second data cut-off after treatment switching from placebo + ADT to darolutamide + ADT is underestimated. Despite the high risk of bias for the results on the basis of the second data cut-off, a high certainty of results for the outcome can be assumed overall. In the overall consideration, this resulted in an indication of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "overall survival" in the present data situation.

This concurs with the company's assessment.

Morbidity

Symptomatic skeletal-related events

Operationalization

The outcome "symptomatic skeletal-related events" was defined in the ARAMIS study as time to occurrence of the first of the following events: external radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumour-related orthopaedic-surgical intervention. Thus, it is a composite outcome, for which analyses of the individual components are necessary for a conclusive interpretation of the results. However, the company did not present these analyses.

Result

A statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "symptomatic skeletal-related events". Due to the high risk of bias and the missing analyses on the individual components, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT.

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Prostate cancer-related invasive procedures

On the basis of the event time analyses, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "prostate cancer-related invasive procedures". Due to the high risk of bias, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT.

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Pain progression (BPI-SF Item 3 or initiation of opioid treatment)

Operationalization

The outcome "pain progression" was defined in the ARAMIS study as time to deterioration in BPI-SF Item 3 by ≥ 2 points from baseline or initiation of treatment with short- or long-acting

opioids. In addition to this prespecified analysis, in Module 4 A, the company presented analyses on pain progression defined as time to deterioration in BPI-SF Item 3 by ≥ 2 points from baseline without considering the initiation of opioid treatment. These analyses were not provided for in the ARAMIS study according to the planning of the study.

The BPI-SF Item 3 refers to the worst pain within the last 24 hours. In the ARAMIS study, the average of the BPI-SF Item 3 of the last 7 days before a study visit, with study visits being conducted every 16 weeks in the course of the study, is determined for both operationalizations of the outcome "pain progression". Hence, pain progression using the BPI-SF Item 3 is recorded at large intervals. Initiation of opioid treatment, in contrast, is continuously recorded in the study via the concomitant medication. In the operationalization with consideration of patients who started opioid treatment, relevant events on pain progression could therefore be recorded that are not recorded using the BPI-SF due to the large intervals between the recordings in the study, as the deterioration at the time of the next visit has already been alleviated by the initiation of opioid treatment. Thus, the operationalization based on the deterioration in the BPI-SF Item 3 or the initiation of opioid treatment is used for the present benefit assessment. The operationalization using the BPI-SF Item 3 alone is presented as supplementary information in the present benefit assessment.

Result

A statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "pain progression" (BPI-SF Item 3 or initiation of opioid treatment). This result is also confirmed in the operationalization using the BPI-SF Item 3 alone, which is presented as supplementary information. Due to the high risk of bias, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "pain progression".

This deviates from the approach of the company, which derived an indication of an added benefit both for the operationalization of BPI-SF Item 3 and for the operationalization of BPI-SF Item 3 or initiation of opioid treatment.

Pain interference (BPI-SF Items 9a–g)

On the basis of the mean differences, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "pain interference" (BPI-SF Items 9a–g). The company did not present an SMD in the form of Hedges' g. Due to missing information on the number of patients included in the analysis, the Institute's calculation of the SMD in the form of Hedges' g is not possible. Thus, an estimation of the relevance of the effect is not possible. Due to the rather small differences in mean values of both treatment groups, a relevant effect is not assumed. This resulted in no hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "pain interference".

This deviates from the approach of the company, which did not consider the outcome "pain interference" in its assessment.

Health status (EQ-5D VAS)

Operationalization

For the present benefit assessment, data on the mean change at week 16 were used for the outcome "health status", recorded using the EQ-5D VAS, as these analyses were based on sufficiently high response rates (91% in the intervention arm and 88% in the control arm). These analyses referred to a notably shorter observation period than the analyses for the other outcomes (except health-related quality of life). According to the original planning of the study, the outcome was to be recorded at baseline, every 16 weeks in the course of the study and at the end of treatment, and follow-up observation was planned every 16 weeks after the end of treatment. This was changed in Protocol Amendment 1 of 24 November 2014 so that the recordings were only conducted at baseline, at week 16 and at the individual end of treatment. Between week 16 and the end of treatment, data for a further time point (week 32), which were recorded before the protocol amendment, are only available for individual patients.

The company additionally presented analyses on the basis of a mixed-effects model repeated measures (MMRM analyses). These analyses are not usable, as the response rates at the end of treatment were only 11% in the intervention arm and 24% in the control arm. The event time analyses presented by the company for improvement or deterioration by ≥ 7 or ≥ 10 points are not usable due to the low response rates in combination with the recordings conducted almost exclusively at week 16 and at the end of treatment (see above). A supplementary presentation of these analyses is therefore not provided in the present benefit assessment.

Result

On the basis of the mean differences at week 16, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "health status" (EQ-5D VAS). The SMD in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was not fully outside the irrelevance range of −0.2 to 0.2, however. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for the outcome "health status" (EQ-5D VAS).

This deviates from the company's approach insofar as the company used analyses of the time to improvement or deterioration of the health status, recorded using the EQ-5D VAS, by ≥ 7 or ≥ 10 points for its assessment. On the basis of these analyses, the company came to the same result.

Health-related quality of life

Operationalization

For the outcome "health-related quality of life", recorded using the FACT-P, responder analyses on the deterioration of the FACT-P total score by ≥ 10 points at week 16 were used for the derivation of the added benefit for the present benefit assessment.

In accordance with the planning of the study, this outcome was only recorded during the double-blind treatment at baseline, at week 16 and at the end of treatment, as was the case for the outcome "health status" (EQ-5D VAS). An exception to this was the prostate cancer-specific subscale of the FACT-P, which, in accordance with the planning of the study, is recorded every 16 weeks during the course of the study and also every 16 weeks after the end of treatment.

Usable data with sufficiently high response rates (89% in the intervention arm and 87% in the control arm) are only available for week 16. These analyses referred to a notably shorter observation period than the analyses for the other outcomes (except for the outcome "health status").

Result

At week 16, a statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "health-related quality of life" (deterioration in the FACT-P total score). Due to the high risk of bias, this resulted in a hint of an added benefit of darolutamide + ADT in comparison with watchful waiting + ADT for this outcome.

This deviates from the company's approach insofar as the company, instead of a hint, derived an indication of an added benefit on the basis of the analyses on the deterioration of the FACT-P total score by ≥ 10 points at week 16. In addition, the company considered the prostate cancer-specific subscale included in the FACT-P separately and derived an indication of an added benefit for the time to deterioration of the subscale by ≥ 3 points at the first data cut-off. In addition to the deterioration, the company also considered the improvement by ≥ 10 points in the total score and the improvement by ≥ 3 points for the prostate cancer-specific subscale for its assessment. From the company's point of view, these analyses did not result in a hint of an added benefit in each case.

Side effects

Operationalization

For the present benefit assessment, the company presented different operationalizations and types of analysis for side effect outcomes.

On the one hand, the company presented analyses on any AEs in the ARAMIS study that included patients with events occurring from the signing of the consent form to randomization. In the ARAMIS study, this period could vary from patient to patient and last up to 28 days. On

the other hand, the company presented analyses on events occurring under treatment. As the first dose of the study medication was administered simultaneously with the randomization, the analyses of the AEs occurring under treatment cover the period relevant for the randomized comparison and were used for the present benefit assessment. The company presented this analysis only for SAEs and discontinuation due to AEs, however. See below for information on the handling of the analyses on the outcome "severe AEs (CTCAE grade ≥ 3)" presented by the company.

The company also presented stratified and unstratified event time analyses according to the factors by which the patients were stratified at randomization. These analyses differ only slightly from each other. For the present benefit assessment, and analogous to the benefit outcomes, the stratified analyses were used for side effect outcomes.

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". Hence, there was no hint of greater or lesser harm from darolutamide + ADT in comparison with watchful waiting + ADT; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which used any SAEs occurring in the study in its assessment, however.

Severe AEs (CTCAE grade ≥ 3)

Operationalization

For the outcome "severe AEs (CTCAE grade ≥ 3)", the company exclusively presented event time analyses of any severe AEs (CTCAE grade ≥ 3) that had occurred in the study at the time of the first data cut-off (i.e. including events from the signing of the consent form to randomization). For severe AEs (CTCAE grade ≥ 3) occurring under treatment, only naive rates at the time of the first data cut-off are available, which are not usable for the present benefit assessment. These rates (273 [28.6%] in the darolutamide + ADT arm and 126 [22.7%] in the placebo + ADT arm) differ only slightly from the naive rates of the severe AEs (CTCAE grade ≥ 3) occurring since the signing of the consent form, with a difference of 7 patients with events in the darolutamide + ADT arm and 11 patients with events in the placebo + ADT arm. For this reason, the event time analyses presented by the company were used for the present benefit assessment.

Result

No statistically significant difference between the treatment groups was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". Hence, there was no hint of greater or lesser harm from darolutamide + ADT in comparison with watchful waiting + ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from darolutamide + ADT in comparison with watchful waiting + ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

A choice of specific AEs on the basis of frequency and differences between the treatment arms is not possible for the present benefit assessment, as the company did not present complete event time analyses for the threshold values required for the choice (see Section 2.4.1). The analyses on the AEs of special interest predefined in the ARAMIS study presented by the company are also not usable for the present benefit assessment, as there is no sufficient information available on the operationalization (see Section 2.4.1).

2.4.4 Subgroups and other effect modifiers

The following potential effect modifier was considered in the present assessment:

- age (< 65 years/65 to < 74 years; 75 to < 84 years; ≥ 85 years)

The characteristic "age" was predefined in the ARAMIS study for the outcomes "MFS" and "overall survival".

Subgroup analyses are available for all outcomes except for the outcomes "pain interference" (BPI-SF Items 9a–g) and "health status" (EQ-5D VAS).

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

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

No effect modifications result from the available subgroup analyses.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented 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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 19).

Determination of the outcome category for symptom outcomes

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. For the outcome "pain progression" (BPI-SF Item 3 or initiation of opioid treatment), the classification is justified below.

For the outcome "pain progression" (BPI-SF Item 3 or initiation of opioid treatment), the supplementary presentation of the operationalization of BPI-SF Item 3 shows that the majority of the events were not due to the initiation of opioid treatment, but to pain progression recorded by deterioration of the BPI-SF Item 3 by ≥ 2 points. It cannot be assumed on the basis of this response criterion alone that patients after pain progression are in a serious range. The company did not present any information on the values the patients with events in the outcome "BPI-SF Item 3" had after pain progression. The outcome "pain progression" (BPI-SF Item 3 or initiation of opioid treatment) was therefore assigned to the outcome category "non-serious/non-severe" for the present benefit assessment.

Table 19: Extent of added benefit at outcome level: darolutamide + ADT vs. watchful waiting + ADT (multipage table)

Outcome category **Outcome**	**Darolutamide + ADT vs. placebo + ADT** **Median time to event (months) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival First data cut-off, 3 September 2018 Second data cut-off, 15 November 2019	NA vs. NA HR: 0.71 [0.50; 0.99] p = 0.045 NA vs. NA HR: 0.69 [0.53; 0.88] p = 0.003 probability: "indication"	Outcome category: mortality $CI_u > 0.85$ added benefit, extent: "considerable"
Morbidity		
Symptomatic skeletal-related events	NA vs. NA HR: 0.43 [0.22; 0.84] p = 0.011 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Prostate cancer-related invasive procedures	NA vs. NA HR: 0.39 [0.25; 0.61] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Pain progression (BPI-SF Item 3[c] or initiation of opioid treatment)	40.3 vs. 25.4 HR: 0.65 [0.53; 0.79] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Pain interference (BPI-SF Items 9a–g)	Mean change: 1.1 vs. 1.3 MD: −0.2 [−0.3; −0.1] ND Hedges' g: –[d]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean change: ND MD: 2.2 [0.2; 4.2] p = 0.028 Hedges' g: 0.12 [0.01; 0.24][e]	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-P total score – deterioration by ≥ 10 points	19.7% vs. 24.5% RR: 0.80 [0.65; 0.99] p = 0.041 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"

Table 19: Extent of added benefit at outcome level: darolutamide + ADT vs. watchful waiting + ADT (multipage table)

Outcome category **Outcome**	**Darolutamide + ADT vs. placebo + ADT** **Median time to event (months) or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	44.4 vs. NA HR: 1.14 [0.91; 1.43] p = 0.263	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)[f]	38.5 vs. NA HR: 1.11 [0.91; 1.36] p = 0.311	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 0.95 [0.67; 1.36] p = 0.791	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Time to first deterioration by ≥ 2 points.
d. Institute's calculation not possible due to missing information.
e. If the CI of Hedges' g 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 inferred.
f. In addition to AEs occurring under the treatment, AEs that occurred between the signing of the informed consent form and randomization are also included.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MD: mean difference; NA: not achieved; ND: no data; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 20 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 20: Positive and negative effects from the assessment of darolutamide + ADT in comparison with watchful waiting + ADT

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of an added benefit – extent: "considerable"	–
Serious/severe symptoms/late complications: ▪ Symptomatic skeletal-related events: hint of an added benefit – extent: "considerable" ▪ Prostate cancer-related invasive procedure: hint of an added benefit – extent: "major"	–
Non-serious/non-severe symptoms/late complications: ▪ Pain progression (BPI-SF Item 3 or initiation of opioid treatment): hint of an added benefit – extent: "considerable"	–
Health-related quality of life: ▪ FACT-P total score – deterioration: hint of an added benefit – extent: "minor"[a]	–
a. With only 16 weeks, the observation period was notably shorter for this outcome than for the other outcomes. ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate	

In the overall consideration, there are exclusively positive effects of darolutamide + ADT in comparison with watchful waiting + ADT for adult men with nmCRPC who are at high risk of developing metastatic disease. An indication of a considerable added benefit was shown for the outcome "overall survival". In addition, there were hints of an added benefit with the extent "considerable" or "major" both for serious/severe symptoms/late complications and for non-serious/non-severe symptoms/late complications. A hint of an added benefit of minor extent was shown for health-related quality of life.

In summary, there is an indication of considerable added benefit of darolutamide in comparison with the ACT "watchful waiting while maintaining ongoing conventional ADT" for men with nmCRPC who are at high risk of developing metastatic disease.

The result of the assessment of the added benefit of darolutamide in comparison with the ACT is summarized in Table 21.

Table 21: Darolutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with non-metastatic castration-resistant prostate cancer who are at high risk of developing metastatic disease[b]	Watchful waiting while maintaining ongoing conventional ADT[c]	Indication of considerable added benefit

a. Presentation of the respective ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the ARAMIS study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
c. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone

The assessment described above concurs with that of the company.

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

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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