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# Darolutamide (prostate cancer) –

## Addendum to Commission A20-43[1]

## Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

**IQWiG employees involved in the addendum**

- Christina Frings
- Ulrich Grouven
- Sabine Ostlender
- Cornelia Rüdig
- Volker Vervölgyi

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ADT | androgen deprivation therapy |
| AE | adverse event |
| BPI-SF | Brief Pain Inventory – Short Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| FACT-P | Functional Assessment of Cancer Therapy-Prostate |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nmCRPC | non-metastatic castration-resistant prostate cancer |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SMD | standardized mean difference |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |

# 1 Background

On 8 September 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-43 (Darolutamide – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented the randomized controlled trial (RCT) ARAMIS for the benefit assessment of darolutamide in adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. This study was used for the benefit assessment for the derivation of the added benefit of darolutamide. In the dossier presented by the company, the information on individual analyses was incomplete in Modules 1 to 4 A, which were used for the assessment on Commission A20-43. The company subsequently submitted these analyses in the framework of the commenting procedure [3-5].

The G-BA needed the assessment of the information presented by the company in the commenting procedure in order to make a decision on the added benefit. The G-BA's commission comprised the following assessments under consideration of the information provided in the company's dossier and the information presented with the comments:

- data on the course of the study
- subcomponents of the outcome "symptomatic skeletal-related events"
- Brief Pain Inventory – Short Form (BPI-SF)
- health-related quality of life recorded using the Functional Assessment of Cancer Therapy-Prostate (FACT-P): prostate cancer-specific subscale
- severe adverse events (AEs)
- specific AEs
- AEs of special interest

The documents presented by the company were used for the present addendum.

In addition to the information provided in Modules 1 to 4 A and the documents subsequently submitted in the commenting procedure, it was necessary to use information from Module 5 of the company's dossier for the present addendum. This was information on study methods and study results. The respective information was included in the present addendum.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

## 2 Assessment

The ARAMIS study included in the benefit assessment is a randomized, double-blind study comparing darolutamide in combination with androgen deprivation therapy (ADT) versus treatment with ADT and the additional administration of placebo. A detailed description of the population, the characteristics of the study and of the interventions, the data cut-offs and the results on the included patient-relevant outcomes can be found in dossier assessment A20-43 [1].

### 2.1 Data on the course of the study

It was noted in dossier assessment A20-43 that there were discrepant data on the median treatment duration at the second data cut-off in Module 4 A of the company's dossier [1]. Furthermore, information on the observation period in the respective study arms and for the individual outcomes was missing in Modules 1 to 4 A of the company's dossier [1]. In addition, information on the treatment discontinuation rates in the comparator arm for the second data cut-off was missing in Modules 1 to 4 A of the dossier [1].

The company subsequently submitted data on the treatment duration and the observation period as well as on treatment discontinuation rates [3,4], which are addressed below.

Table 1 shows the mean and median treatment duration and observation period of the patients and the observation period for individual outcomes if available, under consideration of the data subsequently submitted by the company in the comments. Table 2 contains the data on treatment discontinuation subsequently submitted by the company [3].

Table 1: Information on the course of the study – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Darolutamide + ADT**<br>**N = 955** | **Placebo + ADT**<br>**N = 554** | **Darolutamide + ADT**<br>**N = 955** | **Placebo + ADT**<br>**N = 554** |
|---|---|---|---|---|
| **ARAMIS** | First data cut-off (3 September 2018) | | Second data cut-off (15 November 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] | | | | |
| Mean (SD)[c, d] | 18.7 (9.6)[e] | 17.1 (9.8)[e] | ND | ND |
| Median [min; max][c, d] | 18.2 [0; 46][f] | 15.0 [0; 46][f] | ND | ND |
| Overall survival | ND[g] | ND[g] | ND | ND |
| Morbidity | ND | ND | ND | ND |
| Health-related quality of life | ND | ND | ND | ND |
| Side effects | ND | ND | ND | ND |

a. According to the company, this information refers to the double-blind treatment phase; for the double-blind + open-label treatment phase, the company cites a median treatment duration [months] of 25.8 [0; 59] in the darolutamide + ADT arm vs. 11.0 [1; 12] in the placebo + ADT arm [3].
b. The median overall observation period provided in the publication by Fizazi et al. [6] is 17.9 months at the first data cut-off.
c. Operationalized as time from randomization to the last available entry in the study database.
d. According to the data subsequently submitted by the company [3,4]
e. For the first data cut-off, the CSR contains discrepant data on the mean observation period compared with the data subsequently submitted by the company [3,4]: In the CSR, it is cited as 19.82 (9.55) for the darolutamide + ADT arm vs. 18.23 (9.75) for the placebo + ADT arm [7].
f. For the first data cut-off, the CSR contains discrepant data on the median observation period compared with the data subsequently submitted by the company [3,4]: In the CSR, it is cited as 18.43 [0.1; 46.0] for the darolutamide + ADT arm vs. 16.80 [0.1; 45.6] for the placebo + ADT arm [7].
g. For the outcome "overall survival", transferability of the observation period across outcomes (operationalized as time from randomization to the last available entry in the study database [3]) can be assumed.

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

Table 2: Information on patients with treatment discontinuation until the second data cut-off (15 November 2019) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| Study Characteristic | Double-blind treatment phase | | Double-blind + open-label treatment phase | |
|---|---|---|---|---|
| Category | Darolutamide + ADT N = 955 | Placebo + ADT N = 554 | Darolutamide + ADT N = 955 | Placebo + ADT N = 170[a] |
| **ARAMIS, second data cut-off (15 November 2019)[b]** | | | | |
| Treatment discontinuation total, n (%) | 363 (38.0) | 384 (69.3) | 488 (51.1) | 23 (13.5) |
| Adverse event | 86 (9.0) | 48 (8.7) | 101 (10.6) | 8 (4.7) |
| Confirmed metastasis[c] | 119 (12.5) | 140 (25.3) | 120 (12.6)[d] | 0 (0) |
| Judgment of investigator | 60 (6.3) | 99 (17.9) | 75 (7.9) | 0 (0) |
| Metastasis[c] confirmed by local review[e] | 1 (0.1) | 3 (0.5) | 59 (6.2) | 10 (5.9) |
| Personal reasons | 77 (8.1) | 85 (15.3) | 106 (11.1) | 3 (1.8) |
| Protocol violation | 14 (1.5) | 7 (1.3) | 15 (1.6) | 1 (0.6) |
| Other reasons | 6 (0.6) | 2 (0.4) | 12 (1.3) | 1 (0.6) |
| Patients with treatment discontinuation without metastases total, n (%) | ND | | | |

a. The information in this column refers only to the 170 patients who switched to the intervention arm after the double-blind treatment phase. The 30 patients who remained in the placebo + ADT arm after unblinding and the 354 patients who had already discontinued therapy by the first data cut-off according to Module 4 A of the dossier, Section 4.3.1.2, are not included in the information in this column. The company did not provide an analysis across all patients in the comparator arm for the second data cut-off.
b. According to the data subsequently submitted by the company [3].
c. The metastases were confirmed centrally during the double-blind treatment phase and locally during the open-label treatment phase.
d. According to central scans performed on 22 October 2018, one patient had confirmed metastases during the double-blind treatment phase. The patient discontinued treatment during the open-label treatment phase. Confirmed metastases were documented as the reason for the discontinuation.
e. The patients completed the double-blind treatment at the visit at unblinding, and the scans performed during this visit were assessed by local review.

ADT: androgen deprivation therapy; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

**Treatment duration and treatment discontinuation rates**

It was assumed in dossier assessment A20-43 that the markedly longer treatment duration in the intervention arm was due to differences in treatment discontinuation rates, but information on the second data cut-off was missing to confirm this assumption.

The data subsequently submitted by the company refer at the second data cut-off in the comparator arm to the 170 patients who switched to the intervention after the double-blind treatment phase. The 30 patients who did not choose unblinded therapy with darolutamide + ADT even after the end of the double-blind treatment phase or who discontinued therapy

already during the double-blind treatment phase were not included in the information provided by the company on the comparator arm at the second data cut-off. Hence, data on the treatment discontinuation rates for all included patients are missing for the second data cut-off, so that it can still only be assumed that the markedly longer treatment duration in the intervention arm is due to differences in treatment discontinuation rates.

Besides the missing data on discontinuation rates, it was criticized in dossier assessment A20-43 that there were discrepant data on the median treatment duration at the second data cut-off in Module 4 A of the company's dossier [1,2].

In its comments, the company stated that the treatment duration provided in Table 11 of dossier assessment A20-43 for the second data cut-off referred to the double-blind treatment phase, while the data provided in the footnote referred to the double-blind + open-label treatment phase [3].

The justification of the company that the information on the median treatment durations at the second data cut-off, which were discrepant according to dossier assessment A20-43, was due to the sole consideration of the double-blind treatment phase versus the consideration of the double-blind + open-label treatment phase appears to be conclusive for the intervention arm, but raises questions for the comparator arm: In the comparator arm, the treatment duration would be longer in the sole consideration of the double-blind treatment phase than in the joint consideration of the double-blind + open-label treatment phase. Thus, the cause of the discrepant information on the median treatment duration at the second data cut-off remains unclear.

**Observation period**

In its comments, the company subsequently submitted information on the mean observation period per study arm for the first data cut-off [3]. It did not provide any data on the mean and median observation period per study arm for the second data cut-off. It also did not provide any information on the observation periods of individual patient-relevant outcomes. It argued that, due to the comparable mean observation periods (first data cut-off) for the intervention and comparator arms and the planned 16-weekly contact in the follow-up phase, unsystematic follow-up observation of the patients cannot be assumed [3].

The available data on the mean and median observation periods are presented in Table 1. Information on the observation period per patient-relevant outcome is missing. The general observation periods can only be transferred for the outcome "overall survival", as it can be assumed that this outcome was always recorded in case that follow-up observation was performed. For the other patient-relevant outcomes, however, it is not possible to derive the outcome-specific observation periods from the available data. For them, no information on the actual follow-up observation of the individual outcomes can be derived from the information on the planned follow-up observation either. This is because feedback may not have been provided for every outcome planned for follow-up observation. For the BPI-SF questionnaire,

for example, Section 4.3.1.3.1 in Module 4 A of the dossier shows that there is a rapid and sharp decrease in the response rate, so that – compared with the observation period across outcomes – a markedly shortened observation period can be assumed here. In summary, it is therefore still not possible to assess whether and to what extent there are differences in follow-up observation of the individual outcomes (with the exception of overall survival) between the study arms.

**Summary of the data subsequently submitted on the course of the study**

In the commenting procedure, the company provided data on the course of the study, but the data subsequently submitted were not sufficient to eliminate the uncertainties identified in the dossier assessment. This had no consequence for the present addendum.

## 2.2 Data subsequently submitted on patient-relevant outcomes

In the dossier presented by the company, the information on individual analyses was incomplete in Modules 1 to 4 A, which were used for the assessment on Commission A20-43 (symptomatic skeletal-related events, BPI-SF, FACT-P, AEs). The company subsequently submitted respective data in the commenting procedure [3-5]. In the following, the data subsequently submitted by the company are discussed individually for each of the outcomes concerned; the data on common SAEs and common severe AEs subsequently submitted by the company can be found in Table 10 and Table 11 of Appendix A.

**Morbidity**

***Symptomatic skeletal-related events***

For the outcome "symptomatic skeletal-related events", information on the individual subcomponents was missing for a conclusive interpretation of the results for this outcome in dossier assessment A20-43 [1].

The data subsequently submitted by the company on the individual components of the composite outcome "symptomatic skeletal-related events" are additionally provided in the following Table 3.

Table 3: Results (morbidity, time to event) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| Study<br>Outcome category<br>Outcome<br>Time point | Darolutamide + ADT<br>N | Darolutamide + ADT<br>Median time to first event in the composite outcome in months [95% CI]<br>Patients with event n (%) | Placebo + ADT<br>N | Placebo + ADT<br>Median time to first event in the composite outcome in months [95% CI]<br>Patients with event n (%) | Darolutamide + ADT vs. placebo + ADT<br>HR [95% CI]; p-value[a] |
|---|---|---|---|---|---|
| **ARAMIS** | | | | | |
| **Morbidity** | | | | | |
| Symptomatic skeletal-related events[b] | 955 | NA<br>16 (1.7) | 554 | NA<br>18 (3.2) | 0.43 [0.22; 0.84]; 0.011 |
| External radiotherapy to relieve skeletal symptoms[c] | 955 | NA<br>12 (1.3) | 554 | NA<br>11 (2.0) | –[d] |
| New symptomatic pathologic bone fracture[c] | 955 | NA<br>2 (0.2) | 554 | NA<br>2 (0.4) | –[d] |
| Spinal cord compression[c, e] | 955 | NA<br>0 (0) | 554 | NA<br>3 (0.5) | –[d] |
| Tumour-related orthopaedic-surgical intervention[c] | 955 | NA<br>2 (0.2) | 554 | NA<br>2 (0.4) | –[d] |

a. Effect and confidence interval from Cox proportional hazards model, p-value from log-rank test, each stratified by the factors PSA doubling time ≤ 6 months vs. > 6 months and therapy with bone-sparing substances at randomization: yes vs. no.
b. First data cut-off from 3 September 2018.
c. According to the data subsequently submitted by the company [3,4].
d. Since only the first event within the composite outcome "symptomatic skeletal-related events" was recorded, an effect estimation is not meaningfully interpretable.
e. Data include supplementary information from the CSR [7].

ADT: androgen deprivation therapy; CI: confidence interval; CSR: clinical study report; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PSA: prostate-specific antigen; RCT: randomized controlled trial; vs.: versus

For the individual components of the outcome "symptomatic skeletal-related events", the company presented an analysis in which each patient was included with an event of the individual component only if this was the first event of the composite outcome "symptomatic skeletal-related events". For this reason, conclusions on statistically significant differences in the individual components are not meaningfully interpretable, and they are therefore not presented in Table 3. The results in the individual components do not call into question the result of the composite outcome "symptomatic skeletal-related events". The assessment of the risk of bias of the results of this outcome remains unchanged in comparison with dossier assessment A20-43. In line with dossier assessment A20-43, there is a hint of an added benefit

of darolutamide + ADT in comparison with watchful waiting + ADT due to the high risk of bias.

***Pain progression (BPI-SF Items 9a–9g)***

Dossier assessment A20-43 lacked information on the standardized mean difference (SMD) in the form of Hedges' g for the assessment of the outcome "pain interference" (BPI-SF, Items 9a-g) [1]. Thus, an estimation of the relevance of the effect was not possible. Due to the rather small differences in mean values of both treatment groups, a relevant effect was not assumed, however [1].

The following Table 4 additionally presents the SMD (Hedges' g) subsequently submitted by the company [3] in comparison with dossier assessment A20-43 [1]. The company did not subsequently submit the 95% confidence interval of the SMD (Hedges' g).

Table 4: Results (morbidity, continuous) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| **Study**<br>**Outcome category**<br>**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<br>Hedges' g[e]: −0.12 [ND] |

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. 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. According to the data subsequently submitted by the company [3].

ADT: androgen deprivation therapy; AUC: area under the curve; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; 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

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" recorded with the Items 9a–g of the BPI-SF. It can be inferred from the SMD (Hedges' g) of −0.12 that the corresponding 95% confidence interval cannot be fully outside

the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect was relevant. This resulted in no hint of an added benefit of darolutamide + ADT in comparison with placebo + ADT; an added benefit is therefore not proven. This resulted in no change in comparison with dossier assessment A20-43 [1].

**Health-related quality of life**

***Prostate cancer-specific subscale of the FACT-P***

Dossier assessment A20-43 lacked information on the analysis of patients with event at week 16 for the prostate-specific subscale of the FACT-P [1]. The following Table 5 additionally presents the data subsequently submitted by the company [3,4] in comparison with dossier assessment A20-43 [1].

Table 5: Results (health-related quality of life, dichotomous) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| Study<br>Outcome category<br>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[d] | 882 | 219 (24.8) | 501 | 154 (30.7) | 0.81 [0.68; 0.96] |

a. Patients who received a questionnaire.
b. p-value: unadjusted chi-square test.
c. Deterioration means decrease in score.
d. According to the data subsequently submitted by the company [3,4].

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

The results of the analysis for the prostate-specific subscale of the FACT-P for patients with event at week 16 showed the same direction of effect as the results of the other subscales and the total score of the FACT-P. This resulted in no change for the outcome "FACT-P" in comparison with dossier assessment A20-43 [1].

**Side effects**

***Choice of specific AEs***

In Module 4 A, the company had used threshold values deviating from the requirements for the presentation of common serious AEs (SAEs) and common severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) [1]. It had also stated in Module 4 A that most analyses on AEs of special interest were based on Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) [2]. It was not clear beyond doubt from the information in Module 4 A which of the AEs of special interest defined by the company were prespecified and on which concrete operationalizations the analyses were based. On this basis, a choice of specific AEs was therefore not possible in dossier assessment A20-43 [1]. The open questions could not be clarified in the framework of the oral hearing either [8].

The data subsequently submitted by the company [4] on common SAEs and common severe AEs, using the correct threshold values, are presented in Table 10 and Table 11 of Appendix A. The company presented results for common SAEs and common severe AEs (CTCAE grade ≥ 3) using the specified threshold values [4]; however, it did not present the AEs occurring under treatment, as indicated in the footnotes of its tables subsequently submitted, but analyses that also included patients with events that occurred between the signing of the informed consent form and randomization. As described in dossier assessment A20-43, in the ARAMIS study, this period could vary from patient to patient and last up to 28 days. Dossier assessment A20-43 therefore used analyses of events occurring under treatment [1]. Since the first dose of the study medication was administered at the same time as randomization, these analyses comprised the period relevant for the randomized comparison. A comparison of the number of patients with event for the available data on common SAEs and common severe AEs showed that the number of patients with event differed only slightly between both analyses. Thus, the analyses of any AEs, SAEs and severe AEs presented by the company were used in the present addendum.

The data submitted by the company following the oral hearing showed that, contrary to the information provided in Module 4 A, its analyses of AEs of special interest were not MedDRA SMQs, but compilations of Preferred Terms (PTs) by the company itself [5]. The company indicated which PTs had been included in the respective analyses of AEs of special interest, but referred to SAP Version 4.2 [5], which was only published on 20 September 2018 and thus after the first data cut-off (3 September 2018) [6]. One can only speak of a prespecified analysis if this was defined already before the first data cut-off. For the company's analyses on AEs of special interest, this can be proven from the information in Module 5 for its analysis on bone fracture, but not for its further analyses.

Specific AEs for the present addendum were chosen according to the events that occurred in the relevant study on the basis of frequency and differences between the treatment arms and under consideration of the patient relevance. In addition, specific AEs of particular importance for the disease or for the drugs used in the study could be chosen. On the basis of this method, the following specific AEs were chosen:

- renal and urinary disorders (System Organ Class [SOC], SAEs)
- general disorders and administration site conditions (SOC, SAEs)

***Risk of bias***

The risk of bias of the specific AEs "renal and urinary disorders" (SOC, SAEs) and "general disorders and administration site conditions" (SOC, SAEs) was rated as high. The reasons for this were incomplete observations for potentially informative reasons and differences in the observation periods between the treatment arms.

***Results***

The results of the specific AEs chosen in the present addendum on the basis of the data subsequently submitted by the company are presented in the following Table 6.

Table 6: Results (morbidity, time to event) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| **Study**<br>**Outcome category**<br>**Outcome**<br>**Time point** | **Darolutamide + ADT** | | **Placebo + ADT** | | **Darolutamide + ADT vs. placebo + ADT** |
|---|---|---|---|---|---|
| | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[a]** |
| **ARAMIS** | | | | | |
| **Side effects[b]** | | | | | |
| Renal and urinary disorders (SOC, SAEs) | 954 | NA<br>45 (4.7) | 554 | NA<br>40 (7.2) | 0.58 [0.38; 0.89]; 0.012 |
| General disorders and administration site conditions (SOC, SAEs) | 954 | NA<br>17 (1.8) | 554 | NA<br>1 (0.2) | 9.12 [1.21; 68.56]; 0.032 |

a. Effect and confidence interval from Cox proportional hazards model, p-value from log-rank test, each stratified by the factors PSA doubling time ≤ 6 months vs. > 6 months and therapy with bone-sparing substances at randomization: yes vs. no.
b. According to the data subsequently submitted by the company [4]

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PSA: prostate-specific antigen; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

*Renal and urinary disorders (SOC, SAEs)*

A statistically significant difference in favour of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "renal and urinary disorders" (SOC, SAEs). However, it is questionable whether this effect is actually to be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the disease. The result of

the outcome "renal and urinary disorders" (SOC, SAEs) resulted in a hint of lesser harm of darolutamide + ADT in comparison with the ACT.

*General disorders and administration site conditions (SOC, SAEs)*

A statistically significant difference to the disadvantage of darolutamide + ADT in comparison with placebo + ADT was shown for the outcome "general disorders and administration site conditions" (SOC, SAEs). This resulted in a hint of greater harm from darolutamide + ADT in comparison with the ACT.

## 2.3 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in dossier assessment A20-43 [1] and in Section 2.2 of the present addendum (see Table 7).

**Determination of the outcome category for the outcomes on side effects**

By definition, only SAEs are included in the specific AEs "renal and urinary disorders" (SOC, SAEs) and "general disorders and administration site conditions" (SOC, SAEs). For this reason, these outcomes were assigned to the outcome category of serious/severe side effects.

Table 7: Extent of added benefit at outcome level: darolutamide + ADT vs. watchful waiting + ADT (multipage table)

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

Table 7: Extent of added benefit at outcome level: darolutamide + ADT vs. watchful waiting + ADT (multipage table)

| **Outcome category**<br>**Outcome** | **Darolutamide + ADT vs. placebo + ADT**<br>**Median time to event (months) or proportion of events (%) or mean change**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Side effects** | | |
| SAEs | 44.4 vs. NA<br>HR: 1.14 [0.91; 1.43]<br>p = 0.263 | Greater/lesser harm not proven |
| Severe AEs<br>(CTCAE grade ≥ 3)[e] | 38.5 vs. NA<br>HR: 1.11 [0.91; 1.36]<br>p = 0.311 | Greater/lesser harm not proven |
| Discontinuation due to AEs | NA vs. NA<br>HR: 0.95 [0.67; 1.36]<br>p = 0.791 | Greater/lesser harm not proven |
| Renal and urinary disorders<br>(SOC, SAEs) | NA vs. NA<br>HR: 0.58 [0.38; 0.89]<br>p = 0.012<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>lesser harm, extent: "considerable" |
| General disorders and administration site conditions<br>(SOC, SAEs) | NA vs. NA<br>HR: 9.12 [1.21; 68.56]<br>HR[f]: 0.11 [0.01; 0.83]<br>p = 0.032<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>greater harm, extent: "considerable" |

a. Probability provided if there is a statistically significant and relevant effect.
b. Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval ($CI_u$).
c. Time to first deterioration by ≥ 2 points.
d. 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.
e. In addition to AEs occurring under the treatment, AEs that occurred between the signing of the informed consent form and randomization are also included.
f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; $CI_u$: upper limit of the confidence interval; 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; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

## 2.4 Overall conclusion on added benefit

Table 8 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 8: Positive and negative effects from the assessment of darolutamide + ADT in comparison with watchful waiting + ADT

| **Positive effects** | **Negative effects** |
|---|---|
| Mortality<br>▪ Overall survival: indication of an added benefit – extent: "considerable" | – |
| Serious/severe symptoms/late complications:<br>▪ Symptomatic skeletal-related events: hint of an added benefit – extent: "considerable"<br>▪ Prostate cancer-related invasive procedure: hint of an added benefit – extent: "major" | – |
| Non-serious/non-severe symptoms/late complications:<br>▪ Pain progression (BPI-SF Item 3 or initiation of opioid treatment): hint of an added benefit – extent: "considerable" | – |
| Health-related quality of life:<br>▪ FACT-P total score – deterioration: hint of an added benefit – extent: "minor"[a] | – |
| **Serious/severe side effects[b]:**<br>▪ **Renal and urinary disorders (SAEs): hint of lesser harm – extent: "considerable"** | **Serious/severe side effects:**<br>▪ **General disorders and administration site conditions (SAEs): hint of greater harm – extent: "considerable"** |
| a. With only 16 weeks, the observation period was notably shorter for this outcome than for the other outcomes.<br>b. It is questionable whether the effect is actually to be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the disease.<br>The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments.<br>ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; SAE: serious adverse event | |

With the data subsequently submitted in the comments, there is a hint of lesser harm and a hint of greater harm in side effects in addition to the positive and negative effects presented in dossier assessment A20-43. However, it is questionable whether the positive effect for the outcome "renal and urinary disorders" actually is to be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the disease.

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.

## 2.5 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of darolutamide from dossier assessment A20-43.

The following Table 9 shows the result of the benefit assessment of darolutamide under consideration of dossier assessment A20-43 and the present addendum.

Table 9: 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.<br>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.<br>c. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.<br>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 G-BA decides on the added benefit.

## 3 References

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## Appendix A – Results on side effects

The following tables present events for SOCs and PTs according to MedDRA for the overall rates SAEs and severe AEs (CTCAE grade ≥ 3), each on the basis of the following criteria:

- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

Table 10: Common SAEs[a] – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Darolutamide + ADT**<br>**N = 954** | **Placebo + ADT**<br>**N = 554** |
| **ARAMIS, first data cut-off (3 September 2018)[c]** | | |
| **Overall rate of SAEs** | 237 (24.8) | 111 (20.0) |
| Cardiac disorders | 53 (5.6) | 20 (3.6) |
| Gastrointestinal disorders | 28 (2.9) | 9 (1.6) |
| General disorders and administration site conditions | 17 (1.8) | 1 (0.2) |
| Infections and infestations | 43 (4.5) | 20 (3.6) |
| Pneumonia | 13 (1.4) | 6 (1.1) |
| Injury, poisoning and procedural complications | 19 (2.0) | 10 (1.8) |
| Metabolism and nutrition disorders | 12 (1.3) | 2 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 28 (2.9) | 10 (1.8) |
| Nervous system disorders | 21 (2.2) | 12 (2.2) |
| Renal and urinary disorders | 45 (4.7) | 40 (7.2) |
| Haematuria | 10 (1.0) | 6 (1.1) |
| Urinary retention | 15 (1.6) | 18 (3.2) |
| Respiratory, thoracic and mediastinal disorders | 18 (1.9) | 10 (1.8) |
| Vascular disorders | 12 (1.3) | 5 (0.9) |

a. Events that occurred in ≥ 10 patients in at least one study arm. Events that occurred between the signing of the informed consent form and randomization are also included.
b. MedDRA version 21.0; SOC and PT notation taken from MedDRA without adaptation.
c. According to the data subsequently submitted by the company [4]

ADT: androgen deprivation therapy; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 11: Common severe AEs[a] (CTCAE ≥ 3) – RCT, direct comparison: darolutamide + ADT vs. placebo + ADT

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Darolutamide + ADT**<br>**N = 954** | **Placebo + ADT**<br>**N = 554** |
| **ARAMIS, first data cut-off (3 September 2018)[c]** | | |
| **Overall rate of severe AEs (CTCAE grade ≥ 3)** | 273 (28.6) | 126 (22.7) |
| Blood and lymphatic system disorders | 15 (1.6) | 9 (1.6) |
| Cardiac disorders | 48 (5.0) | 15 (2.7) |
| Gastrointestinal disorders | 22 (2.3) | 12 (2.2) |
| General disorders and administration site conditions | 22 (2.3) | 7 (1.3) |
| Infections and infestations | 43 (4.5) | 18 (3.2) |
| Pneumonia | 10 (1.0) | 4 (0.7) |
| Injury, poisoning and procedural complications | 20 (2.1) | 10 (1.8) |
| Investigations | 19 (2.0) | 7 (1.3) |
| Metabolism and nutrition disorders | 25 (2.6) | 12 (2.2) |
| Musculoskeletal and connective tissue disorders | 18 (1.9) | 7 (1.3) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 24 (2.5) | 11 (2.0) |
| Nervous system disorders | 21 (2.2) | 15 (2.7) |
| Renal and urinary disorders | 47 (4.9) | 37 (6.7) |
| Haematuria | 10 (1.0) | 8 (1.4) |
| Urinary retention | 15 (1.6) | 11 (2.0) |
| Respiratory, thoracic and mediastinal disorders | 23 (2.4) | 11 (2.0) |
| Vascular disorders | 37 (3.9) | 23 (4.2) |
| Hypertension | 30 (3.1) | 16 (2.9) |

a. Events that occurred in ≥ 10 patients in at least one study arm. Events that occurred between the signing of the informed consent form and randomization are also included.
b. MedDRA version 21.0; SOC and PT notation taken from MedDRA without adaptation.
c. According to the data subsequently submitted by the company [4]

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus