Darolutamide (prostate cancer)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Darolutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

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

IQWiG thanks the respondent and the patient organization 'Bundesverband Prostatakrebs Selbsthilfe' for participating in the written exchange and for their support. The respondent and the 'Bundesverband Prostatakrebs Selbsthilfe' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BFI	Brief Fatigue Inventory
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer-associated gene
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-P	Functional Assessment of Cancer Therapy-Prostate
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)
PT	Preferred Term
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

The Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug darolutamide (in combination with androgen deprivation therapy) in accordance with §35a Social Code Book (SGB) V. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 13 August 2025.

Research question

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

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a, b]
Adult men with metastatic hormone-sensitive prostate cancer	▪ Conventional ADT[c] in combination with apalutamide or ▪ Conventional ADT[c] in combination with enzalutamide or ▪ Conventional ADT[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer) or ▪ Conventional ADT[c] in combination with darolutamide and docetaxel or
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, in the present therapeutic indication, it is assumed that combination therapy – additional therapy to conventional ADT – is usually an option for the patients, taking into account any comorbidities and the general condition. c. In the context of the present therapeutic indication, conventional ADT refers to surgical or medicinal castration by therapy 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 of 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.

Study pool and study design

Concurring with the company, the review of the completeness of the study pool did not identify any studies of a direct comparison of darolutamide + ADT versus the ACT in the given therapeutic indication.

Therefore, the company conducted a literature search for randomized controlled trials (RCTs) for an adjusted indirect comparison according to Bucher. On the intervention side, the company identified the ARANOTE study comparing darolutamide + ADT versus placebo + ADT. On the ACT side, the company identified 4 studies:

- TITAN (apalutamide + ADT versus placebo + ADT)
- LATITUDE (abiraterone acetate + prednis[ol]one + ADT versus placebo + ADT)
- ARCHES and China ARCHES (enzalutamide + ADT versus placebo + ADT).

However, the company decided to conduct the indirect comparison only for ARANOTE and TITAN and thus for the comparison of darolutamide + ADT versus apalutamide + ADT via placebo + ADT as common comparator.

The ACT options specified by the G-BA were considered equally appropriate; a comparison exclusively versus the option of apalutamide + ADT was therefore appropriate. As the company only presented an indirect comparison versus the treatment option of apalutamide + ADT, the review of the completeness of the company's study pool on the ACT side was limited to this treatment option.

The review of the study pool did not identify any additional relevant studies for the adjusted indirect comparison presented by the company.

ARANOTE (study with darolutamide + ADT)

The ARANOT study is an ongoing, double-blind RCT comparing darolutamide + ADT versus placebo + ADT. The study included adult men with metastatic hormone-sensitive prostate cancer. Patients with regional lymph node metastases only or with known brain/leptomeningeal metastases were not included. Patients had to be in a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2. Furthermore, patients had to have started ADT (a gonadotropin-releasing hormone [GnRH] agonist/antagonist or surgical castration) within 12 weeks prior to randomization. Prior treatment for prostate cancer with chemotherapy, including docetaxel, was not allowed.

A total of 669 patients were included in the ARANOTE study and randomly allocated in a 2:1 ratio either to treatment with darolutamide + ADT (N = 446) or to placebo + ADT (N = 223).

Randomization was stratified according to presence versus absence of visceral metastases, as well as prior local therapy versus no prior local therapy.

Treatment with darolutamide was largely in compliance with the summary of product characteristics (SmPC). Patients in both study arms had to continue the previously started ADT during the study.

Treatment was given until radiological disease progression, withdrawal of consent or unacceptable toxicity; continued treatment beyond progression was possible at the investigator's discretion.

The primary outcome of ARANOTE was radiographic progression-free survival (rPFS). Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

TITAN (study with apalutamide + ADT)

The TITAN study is an ongoing, double-blind RCT comparing apalutamide + ADT versus placebo + ADT. The study included adult men with metastatic hormone-sensitive prostate cancer, with the presence of metastases in the form of ≥ 1 documented bone lesion. Patients with brain metastases were excluded from the study. The patients had to have a good general condition corresponding to an ECOG PS ≤ 1. Furthermore, patients had to have started ADT (a GnRH agonist/antagonist or surgical castration) ≥ 14 days prior to randomization. Prior treatment with ≤ 6 cycles of docetaxel was also permitted.

A total of 1052 patients were included in the TITAN study and randomly allocated in a 1:1 ratio either to treatment with apalutamide + ADT (N = 525) or to placebo + ADT (N = 527). Randomization was stratified according to Gleason score (≤ 7 versus > 7), geographical region (North America and Europe versus other countries) and prior docetaxel use (yes versus no).

Treatment with apalutamide was largely in compliance with the SmPC. Patients in both study arms had to continue the previously started ADT during the study.

Treatment was given until disease progression, withdrawal of consent or unacceptable toxicity. At the investigator's discretion, treatment could be continued beyond radiological progression until the occurrence of clinical progression.

The primary outcomes of the TITAN study were overall survival and rPFS. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Similarity of the studies for the indirect comparison

Overall, there were some differences in the study and patient characteristics between ARANOTE and TITAN, but none of them fundamentally called into question their similarity for conducting an adjusted indirect comparison via the common comparator placebo + ADT.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

In the given situation, an indirect comparison could only be conducted for the outcome of overall survival, as only for this outcome were data with sufficient certainty of results available in both studies, allowing an informative adjusted indirect comparison to be conducted.

There was one RCT on each side of the available adjusted indirect comparison. Consequently, there was no need to assess homogeneity. As there was no study of direct comparison of darolutamide + ADT versus the ACT, it was impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, no more than hints, e.g. of an added benefit, could be derived on the basis of the data available from the adjusted indirect comparison.

Results

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between darolutamide + ADT versus apalutamide + ADT for the outcome overall survival. There is no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Morbidity

Worst pain, symptomatic skeletal-related events, fatigue, health status

There were no suitable data for the outcomes in the category of worst pain (recorded using the Brief Pain Inventory-Short Form [BPI-SF] Item 3), symptomatic skeletal-related events, fatigue (recorded using the Brief Fatigue Inventory [BFI]) and health status (recorded using EQ-5D visual analogue scale [VAS]). In each case, there is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Pain interference

Due to insufficient certainty of results in the ARANOTE study, it was not possible to conduct an indirect comparison for the outcome of pain interference (recorded using the BPI-SF Item

9a–9g). There is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Health-related quality of life

No suitable data were available for the outcome of health-related quality of life, recorded using the Functional Assessment of Cancer Therapy-Prostate (FACT-P). There is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Side effects

Due to the insufficient certainty of results in ARANOTE and TITAN, it was not possible to conduct an indirect comparison for the outcomes in the side effects category. In each case, there is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit 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 + ADT in comparison with the ACT are assessed as follows:

Overall, based on the adjusted indirect comparison using the common comparator of placebo + ADT, there are neither positive nor negative effects of darolutamide + ADT in comparison with apalutamide + ADT. However, it should be noted that usable results with sufficient certainty of results for an indirect comparison were only available for the outcome overall survival.

In summary, there is no hint of an added benefit of darolutamide + ADT versus apalutamide + ADT for adult men with metastatic hormone-sensitive prostate cancer.

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

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

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

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult men with metastatic hormone-sensitive prostate cancer	▪ Conventional ADT[c] in combination with apalutamide or ▪ Conventional ADT[c] in combination with enzalutamide or ▪ Conventional ADT[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer) or ▪ Conventional ADT[c] in combination with darolutamide and docetaxel or	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, in the present therapeutic indication, it is assumed that combination therapy – additional therapy to conventional ADT – is usually an option for the patients, taking into account any comorbidities and the general condition.
c. In the context of the present therapeutic indication, conventional ADT refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists.

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

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

I 2 Research question

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

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a, b]
Adult men with metastatic hormone-sensitive prostate cancer	▪ Conventional ADT[c] in combination with apalutamide or ▪ Conventional ADT[c] in combination with enzalutamide or ▪ Conventional ADT[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer) or ▪ Conventional ADT[c] in combination with darolutamide and docetaxel or
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, in the present therapeutic indication, it is assumed that combination therapy – additional therapy to conventional ADT – is usually an option for the patients, taking into account any comorbidities and the general condition. c. In the context of the present therapeutic indication, conventional ADT refers to surgical or medicinal castration by therapy 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 of 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. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study lists on darolutamide (status: 2 June 2025)
- Bibliographical literature search on darolutamide (last search on 2 June 2025)
- Search of trial registries / trial results databases for studies on darolutamide (last search on 2 June 2025)
- Search on the G-BA website for darolutamide (last search on 2 June 2025)
- Bibliographical literature search on the ACT (last search on 2 June 2025)
- Search of trial registries/trial results databases for studies on the ACT (last search on 2 June 2025)
- Search on the G-BA website for the ACT (last search on 2 June 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on darolutamide (last search on 21 August 2025); for search strategies, see I Appendix A of the full dossier assessment
- Search of trial registries for studies on apalutamide (last search on 8 September 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the review of the completeness of the study pool did not identify any studies of a direct comparison of darolutamide + ADT versus the ACT in the given therapeutic indication.

Therefore, the company conducted a literature search for randomized controlled trials (RCTs) for an adjusted indirect comparison according to Bucher [3]. On the intervention side, the company identified the ARANOTE study comparing darolutamide + ADT versus placebo + ADT. On the ACT side, the company identified 4 studies:

- TITAN (apalutamide + ADT versus placebo + ADT)
- LATITUDE (abiraterone acetate + prednis[ol]one + ADT versus placebo + ADT)
- ARCHES and China ARCHES (enzalutamide + ADT versus placebo + ADT).

However, the company decided to conduct the indirect comparison only for ARANOTE and TITAN and thus for the comparison of darolutamide + ADT versus apalutamide + ADT via placebo + ADT as common comparator.

The ACT options specified by the G-BA (see Table 4) were considered equally appropriate; a comparison exclusively versus the option of apalutamide + ADT was therefore appropriate. As the company only presented an indirect comparison versus the treatment option of apalutamide + ADT, the review of the completeness of the company's study pool on the ACT side was limited to this treatment option.

The review of the study pool did not identify any additional relevant studies for the adjusted indirect comparison presented by the company.

I 3.1 **Studies included**

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
darolutamide + ADT vs. placebo + ADT						
21140 (ARANOTE[d])	Yes	Yes	No	Yes [4]	Yes [5-7]	Yes [8]
apalutamide + ADT vs. placebo + ADT						
CR107614 (TITAN[d])	No	No	Yes	No	Yes [9-11]	Yes [12-20]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

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

The study pool for the benefit assessment concurred with that of the company. The TITAN study had already been presented and assessed in a previous benefit assessment of apalutamide + ADT [20].

Figure 1 is a schematic representation of the indirect comparison.

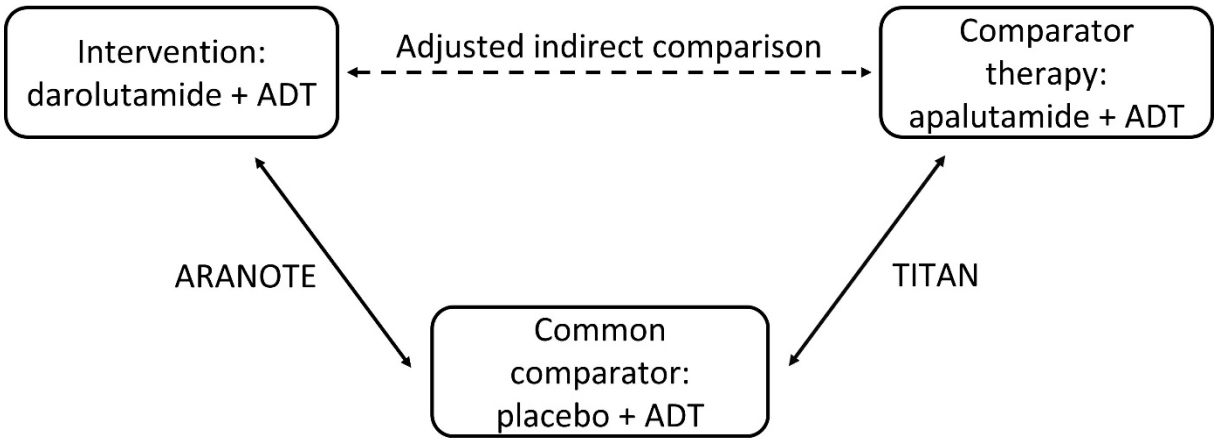

Figure 1: Study pool for the adjusted indirect comparison between darolutamide + ADT versus apalutamide + ADT via the common comparator placebo + ADT

I 3.2 **Study characteristics**

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
darolutamide + ADT vs. placebo + ADT						
ARANOTE	RCT, double-blind, parallel	Adult patients with metastatic[b] hormone-sensitive prostate cancer ▪ ECOG PS ≤ 2	darolutamide + ADT (N = 446) placebo + ADT (N = 223)	Screening: up to 28 days Treatment: until disease progression[c], withdrawal of consent, unacceptable toxicity, investigator's decision, start of new anticancer treatment Observation[d]: outcome-specific, at most until death, withdrawal of consent, lost to follow-up or end of study	133 study centres in: Australia, Brazil, Canada, Chile, China, India, Latvia, Lithuania, New Zealand, Peru, Russia, South Africa, Spain, Taiwan, Ukraine 2/2021–ongoing Data cut-offs: 7 June 2024[e] 10 January 2025[f]	Primary: rPFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
apalutamide + ADT vs. placebo + ADT						
TITAN	RCT, double-blind, parallel	Adult patients with metastatic[g] hormone-sensitive prostate cancer ▪ ECOG PS ≤ 1[h]	apalutamide + ADT (N = 525) placebo + ADT (N = 527)	Screening: up to 28 days Treatment: until disease progression[c], withdrawal of consent, unacceptable toxicity Observation[d]: outcome-specific, at most until death, withdrawal of consent, lost to follow-up or end of study	260 study centres in: Argentina, Australia, Brazil, Canada, China, Czech Republic, France, Germany, Great Britain, Hungary, Israel, Japan, Mexico, Poland, Romania, Russia, South Korea, Spain, Sweden, Turkey, Ukraine, United States 12/2015–ongoing Data cut-offs: 23 November 2018[i] 7 September 2020[j]	Primary: overall survival, rPFS Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients with regional lymph node metastases only or with known brain/leptomeningeal metastases were not included.
c. Continuing treatment beyond radiological progression was possible at the discretion of the investigator.
d. Outcome-specific information is provided in Table 8.
e. The primary rPFS analysis or interim analysis for the outcome overall survival was planned after approximately 214 rPFS events or approximately 145 deaths. After this data cut-off, patients were unblinded and were allowed to switch from placebo + ADT to darolutamide + ADT.
f. The final analysis for the outcome overall survival was planned after approximately 180 deaths.
g. Patients with brain metastases or exclusively lymph node or visceral metastases were excluded.
h. Until Amendment 1 to the study protocol, patients with an ECOG PS of 2 were also eligible for inclusion.
i. Prespecified interim analysis on the outcome overall survival and final analysis on the rPFS outcome, planned after approximately 205 deaths; after this data cut-off, the study was unblinded following an IDMC recommendation, and patients from the control arm were allowed to switch to treatment with apalutamide in an extension phase.
j. Prespecified final analysis for the outcome overall survival, planned after approximately 410 deaths.

Table 6: Characteristics of the studies included – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ADT: androgen deprivation therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IDMC: independent data monitoring committee; N: number of randomized patients; RCT: randomized controlled trial; rPFS: radiological progression-free survival						

Table 7: Characteristics of the intervention – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study	Intervention	Comparison
darolutamide + ADT vs. placebo + ADT		
ARANOTE	darolutamide 600 mg twice daily, orally + ADT[a]	placebo, twice daily, orally + ADT[a]
	Dose modifications ▪ darolutamide/placebo: largely in compliance with the SmPC ▪ ADT: It was possible to switch to a GnRH agonist/antagonist.	
	Disallowed prior treatment ▪ GnRH agonist/antagonist > 12 weeks before randomization[b] ▪ Second-generation androgen inhibitors (e.g. enzalutamide, darolutamide, apalutamide) or other investigational androgen inhibitors ▪ CYP17 enzyme inhibitors (e.g. abiraterone acetate) or oral ketoconazole as anticancer treatment for prostate cancer ▪ Chemotherapy, including docetaxel, or immunotherapy for prostate cancer ▪ Systemic corticosteroids with a dose > 10 mg of prednisone/day within 28 days prior to randomization ▪ Radiopharmaceuticals ▪ Any other anticancer treatment for prostate cancer, excluding local therapies and androgen deprivation therapy ▪ Radiotherapy (external beam radiation therapy, brachytherapy) or radiopharmaceutical agents within 2 weeks before randomization ▪ Investigational products within 28 days before randomization **Allowed concomitant treatment** ▪ Analgesics including opioids ▪ Palliative radiation therapy, surgical intervention ▪ For osteoporosis: continuation of prior treatment with osteoclast-targeted therapy **Disallowed concomitant treatment** ▪ Other systemic anticancer therapies or other investigational products ▪ Radiopharmaceuticals ▪ Immunotherapy (e.g. sipuleucel-T) ▪ Cytotoxic chemotherapy including docetaxel ▪ enzalutamide, apalutamide, bicalutamide, flutamide, nilutamide ▪ abiraterone acetate or other CYP17 inhibitors ▪ Systemic ketoconazole or other therapies for the treatment of prostate cancer[c] (excluding local therapies) ▪ Live, attenuated, replication-competent vaccines	

Table 7: Characteristics of the intervention – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study	Intervention	Comparison
apalutamide + ADT vs. placebo + ADT		
TITAN	apalutamide 240 mg orally daily + ADT[d]	placebo orally daily + ADT[d]
	Dose modifications: ▪ apalutamide/placebo: largely in compliance with the SmPC ▪ ADT: no modification allowed	
	Allowed prior treatment ▪ Prior treatment with docetaxel for mHSPC: maximum of 6 cycles, maintenance of response (confirmed by imaging and PSA test); last dose ≤ 2 months prior to randomization ▪ Maximum of 1 course of radiation or surgical intervention; radiation therapy for metastatic lesions must be completed prior to randomization ▪ Prior treatments for localized prostate cancer (all treatments must have been completed ≥ 1 year prior to randomization): ≤ 3 years total of ADT, and other forms of therapies including radiation therapy, prostatectomy, lymph node dissection and systemic therapies **Disallowed prior treatment** ▪ Other next-generation anti-androgens (e.g. enzalutamide), CYP17 inhibitors (e.g. abiraterone acetate), immunotherapy (e.g. sipuleucel-T), radiopharmaceutical agents ▪ Other investigational products or invasive surgical procedure (not including castration) within 28 days prior to randomization **Allowed concomitant treatment** ▪ Continuation of treatment with bisphosphonates or denosumab for bone metastases if dose was stable for ≥ 28 days prior to randomization; otherwise only after documented progression; doses for prevention of osteoporosis allowed ▪ Intermittent use of opioids for pain control ▪ Surgical interventions or procedures for the management of complications due to local progression (e.g. transurethral resection of the prostate and placement of urethral stents) ▪ Other supportive therapies, e.g. haematopoietic growth factors, transfusions **Disallowed concomitant treatment** ▪ Drugs known to lower the seizure threshold, from 28 days prior to randomization ▪ CYP17 inhibitors (e.g. abiraterone acetate) other hormonal agents for the treatment of prostate cancer, other anti-androgens (e.g. enzalutamide, bicalutamide, nilutamide, flutamide, cyproterone acetate) ▪ Chemotherapy, immunotherapy for cancer treatment, other antineoplastic agents ▪ Other investigational products ▪ Radiation therapy for new painful metastases that were not present at baseline	

Table 7: Characteristics of the intervention – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study	Intervention	Comparison
a. Treatment with GnRH agonists or antagonists or surgical castration, with or without first-generation anti-androgens, which started ≤ 12 weeks before randomization. For patients receiving a GnRH agonist, treatment in combination with a first-generation anti-androgen for ≥ 14 days prior to randomization was recommended. The anti-androgen had to be discontinued ≥ 1 day before the start of the study treatment. b. Except neoadjuvant and/or adjuvant therapy for a duration ≤ 24 months and completed ≥ 12 months prior to randomization. c. Any new systemic anticancer therapy could be initiated ≥ 7 days after the last dose of study drug. d. Treatment with GnRH agonists or antagonists or surgical castration must have been started ≥ 14 days prior to randomization (treatment before randomization for ≤ 6 months). Patients who started a GnRH agonist ≤ 28 days prior to randomization were required to take a first-generation anti-androgen for ≥ 14 days prior to randomization. The anti-androgen had to be discontinued prior to randomization. ADT: androgen deprivation therapy; CYP: cytochrome P450; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; RCT: randomized controlled trial		

Study design

ARANOTE (study with darolutamide + ADT)

The ARANOT study is an ongoing, double-blind RCT comparing darolutamide + ADT versus placebo + ADT. The study included adult men with metastatic hormone-sensitive prostate cancer. Patients with regional lymph node metastases only or with known brain/leptomeningeal metastases were not included. Patients had to be in a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2. Furthermore, patients had to have started ADT (a gonadotropin-releasing hormone [GnRH] agonist/antagonist or surgical castration) within 12 weeks prior to randomization. Prior treatment for prostate cancer with chemotherapy, including docetaxel, was not allowed.

A total of 669 patients were included in the ARANOTE study and randomly allocated in a 2:1 ratio either to treatment with darolutamide + ADT (N = 446) or to placebo + ADT (N = 223). Randomization was stratified according to presence versus absence of visceral metastases, as well as prior local therapy versus no prior local therapy.

Treatment with darolutamide was largely in compliance with the summary of product characteristics (SmPC) [21]. Patients in both study arms had to continue the previously started ADT during the study. For patients receiving a GnRH agonist as ADT, treatment in combination with a first-generation anti-androgen for at least 14 days prior to randomization was recommended. The anti-androgen had to be discontinued at least 1 day before the start of the study treatment. Switching to a GnRH agonist/antagonist during the study was permitted.

Treatment was given until radiological disease progression, withdrawal of consent or unacceptable toxicity; continued treatment beyond progression was possible at the investigator's discretion.

After the primary analysis of the outcome radiological progression-free survival (rPFS), in the event of a positive benefit-risk assessment, an open-label phase was planned, in which patients in the control arm could switch to treatment with darolutamide + ADT.

The primary outcome of ARANOTE was rPFS. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

TITAN (study with apalutamide + ADT)

The TITAN study is an ongoing, double-blind RCT comparing apalutamide + ADT versus placebo + ADT. The study included adult men with metastatic hormone-sensitive prostate cancer, with the presence of metastases in the form of ≥ 1 documented bone lesion. Patients with brain metastases were excluded from the study. The patients had to have a good general condition corresponding to an ECOG PS ≤ 1. Furthermore, patients had to have started ADT (a GnRH agonist/antagonist or surgical castration) ≥ 14 days prior to randomization. Prior treatment with ≤ 6 cycles of docetaxel in the stage of metastatic hormone-sensitive prostate cancer was also permitted.

A total of 1052 patients were included in the TITAN study and randomly allocated in a 1:1 ratio either to treatment with apalutamide + ADT (N = 525) or to placebo + ADT (N = 527). Randomization was stratified according to Gleason score (≤ 7 versus > 7), geographical region (North America and Europe versus other countries) and prior docetaxel use (yes versus no).

Treatment with apalutamide was largely in compliance with the SmPC [22]. Patients in both study arms had to continue the previously started ADT during the study. Patients who had started a GnRH agonist ≤ 28 days prior to randomization were required to receive a combination treatment with a first-generation anti-androgen for ≥ 14 days prior to randomization. The anti-androgen had to be discontinued prior to randomization.

Treatment was given until disease progression, withdrawal of consent or unacceptable toxicity. At the investigator's discretion, treatment could be continued beyond radiological progression until the occurrence of clinical progression.

In the event of a positive study result, an open-label extension phase was planned in which patients in the control arm could switch to treatment with apalutamide + ADT.

The primary outcomes of the TITAN study were overall survival and rPFS. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Data cuts

ARANOTE

The following data cuts were available for the ARANOTE study:

- 1st data cut (7 June 2024):
  Prespecified primary analysis for the outcome rPFS or interim analysis for the outcome overall survival, planned after approx. 214 rPFS events or approx. 145 deaths; after this data cut-off, patients were unblinded and it was possible to switch treatment from placebo + ADT to darolutamide + ADT.
- 2nd data-cut (10 January 2025):
  Prespecified final analysis for the outcome overall survival, planned after approximately 180 deaths

TITAN

The following data cuts were available for the TITAN study:

- 1st data cut (23 November 2018):
  Prespecified interim analysis for the outcome overall survival and final analysis on the outcome rPFS, planned after approx. 205 deaths; after this data cut-off, the study was unblinded and it was possible for patients in the control arm to switch to treatment with apalutamide + ADT.
- 2nd data-cut (7 September 2020):
  Prespecified final analysis for the outcome overall survival, planned after approximately 410 deaths

Data cuts for the indirect comparison

In Module 4, the company presented the results from the first data cuts for the indirect comparison of ARANOTE and TITAN. For the ARANOTE study, the company justified this with the fact that 27% of the patients in the control arm had started treatment with darolutamide + ADT at the 2nd data cut-off and that the data cut was therefore potentially highly biased. The company presented the results on the outcomes overall survival and side effects for the 2nd data cut in Module 4 Appendix 4 G. For the TITAN study, the company did not mention in Module 4 that there was also a 2nd data cut. About 40% of the patients in the control arm had started treatment with apalutamide + ADT at the time of the 2nd data cut-off.

Performing an indirect comparison of the 2 studies ARANOTE and TITAN at the first data cut-off was assessed as suitable. In both studies, this data cut-off took place approximately 3 years after baseline, and in each case it was the last time point before the study was unblinded and patients had the option to switch from placebo + ADT to treatment in the intervention arm.

Therefore, the results presented by the company on the first data cuts of ARANOTE and TITAN were used for this benefit assessment.

Planned duration of follow-up

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

Table 8: Planned duration of follow-up– RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up**
darolutamide + ADT vs. placebo + ADT	
ARANOTE	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or end of study
Morbidity	
Symptomatic skeletal-related events	Up to 12 months after the last dose of the study medication or the end of the double-blind study phase
Pain (BPI-SF)	Up to 12 months after the last dose of the study medication or the end of the double-blind study phase
Health-related quality of life	
FACT-P	Up to 12 months after the last dose of the study medication or the end of the double-blind study phase
Side effects	Up to 30 days after the last dose of the study medication[a]
apalutamide + ADT vs. placebo + ADT	
TITAN	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up or end of study
Morbidity	
Symptomatic skeletal-related events	Until death, withdrawal of consent, lost to follow-up or end of study
Pain (BPI-SF)	Up to 12 months after the last dose of the study medication
Fatigue (BFI)	Up to 12 months after the last dose of the study medication
Health status (EQ-5D VAS)	Up to 12 months after the last dose of the study medication
Health-related quality of life	
FACT-P	Up to 12 months after the last dose of the study medication
Side effects	Up to 30 days after the last dose of the study medication[a]

a. Treatment-related SAEs were recorded until death, lost to follow-up, withdrawal of consent or end of study.

ADT: androgen deprivation therapy; BPI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In both studies, the observation periods for the outcomes in the categories of morbidity and health-related quality of life (except the outcome symptomatic skeletal-related events in the

TITAN study) were systematically shortened. According to the study design, these outcomes were to be observed for up to 12 months after the last dose of study medication (or the end of the double-blind study phase in the ARANOTE study). Thus, although the planned observation periods of these outcomes did not cover the entire study period, it was positive to note that they were at least recorded for 12 months beyond the end of the study treatment.

With the exception of treatment-related serious adverse events (SAEs), the observation periods for the outcomes in the side effects category were also systematically shortened. These outcomes were only recorded for the period of treatment with the study medication (plus 30 days).

However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Patient characteristics

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

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study Characteristic	**darolutamide + ADT vs. placebo + ADT**		**apalutamide + ADT vs. placebo + ADT**	
Category	**ARANOTE**		**TITAN**	
	darolutamide + ADT	**Placebo + ADT**	**apalutamide + ADT**	**Placebo + ADT**
	N[a] = 446	**N[a] = 223**	**N[a] = 525**	**N[a] = 527**
Age [years], mean (SD)	70 (9)	69 (9)	69 (8)	68 (8)
Family origin, n (%)				
White	251 (56)	125 (56)	354 (67)	365 (69)
Black or African American	41 (9)	24 (11)	10 (2)	9 (2)
Asian	144 (32)	65 (29)	119 (23)	110 (21)
Other	10 (2)	9 (4)	31 (6)[b]	35 (7)[b]
Unknown	0 (0)	0 (0)	11 (2)	8 (2)
ECOG PS, n (%)				
0	235 (53)	98 (44)	328 (63)	348 (66)
1	199 (45)	117 (53)	197 (38)	178 (34)
2	12 (3)	8 (4)	0 (0)	1 (< 1)
Visceral metastases[c], n (%)	53 (12)	27 (12)	56 (11)	72 (14)
Bone metastases, n (%)	344 (77)	171 (77)	525 (100)	527 (100)

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study Characteristic Category	darolutamide + ADT vs. placebo + ADT		apalutamide + ADT vs. placebo + ADT	
	ARANOTE		TITAN	
	darolutamide + ADT	Placebo + ADT	apalutamide + ADT	Placebo + ADT
	N[a] = 446	N[a] = 223	N[a] = 525	N[a] = 527
Gleason score, n (%)				
< 8	122 (27)	67 (30)	174 (33)	169 (32)
≥ 8	311 (70)	146 (66)	351 (67)	358 (68)
Missing	13 (3)	10 (5)	0 (0)	0 (0)
Disease volume, n (%)				
High[d]	315 (71)	157 (70)	325 (62)	335 (64)
Low	131 (29)	66 (30)	200 (38)	192 (36)
Duration of prior ADT before randomization [months]				
Median [Q1; Q3]	1.1 [ND; ND][e]	0.9 [ND; ND][e]	1.8 [0.9; 3.5]	1.8 [0.9; 3.5]
Median [min; max]	1.1 [0.0; 2.8][e]	0.9 [0.0; 2.8][e]	1.8 [ND; ND]	1.8 [ND; ND]
Prior docetaxel treatment, n (%)	0 (0)	0 (0)	58 (11)	55 (10)
Prior radiotherapy / prostatectomy, n (%)	87 (20)	50 (22)	94 (17)	79 (15)
Time between first diagnosis and randomization [months]				
Mean (SD)	11.0 (27.6)	13.4 (37.5)	15.1 (31.8)	11.3 (26.2)
Median [min; max]	2.6 [0.3; 186.6]	2.4 [0.5; 339.2]	4.1 [0.5; 222.9]	4.0 [0.7; 341.4]
Time between diagnosis of a metastasis and randomization [months]				
Mean (SD)	3.0 (6.5)	2.1 (1.4)	3.5 (3.0)	3.4 (2.4)
Median [min; max]	1.9 [0.2; 90.6]	1.8 [0.3; 9.6]	2.6 [0.5; 28.2]	2.7 [0.4; 27.1]
Treatment discontinuation, n (%)[f]	203 (46)	160 (72)	177 (34)	284 (54)
Progression	120 (27)	101 (45)	99 (19)	277 (53)
Withdrawal of consent by the patient	34 (8)	22 (10)	22 (4)	23 (4)
AE	28 (6)	22 (10)	39 (7)	17 (3)
Death	9 (2)	3 (1)	8 (2)	13 (3)
Never received study medication	3 (< 1)	0 (0)	1 (< 1)	0 (0)
Study discontinuation, n (%)	ND	ND	ND	ND

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Study Characteristic Category	darolutamide + ADT vs. placebo + ADT		apalutamide + ADT vs. placebo + ADT	
	ARANOTE		TITAN	
	darolutamide + ADT	Placebo + ADT	apalutamide + ADT	Placebo + ADT
	N[a] = 446	N[a] = 223	N[a] = 525	N[a] = 527

a. Values that are based on other patient numbers are marked in the corresponding line.
b. Includes American Indian or Alaska Native, multiple and other; Institute's calculation.
c. ARANOTE: confirmed by central review; TITAN: unclear whether central confirmation took place.
d. According to the S3 guideline, high-volume disease includes patients with at least 4 bone metastases, of which at least 1 metastasis outside of the axial skeleton or pelvis, and/or visceral metastases.
e. Within 12 weeks before randomization; Institute's calculation from data in days; data for N = 398 in the intervention arm and N = 198 in the control arm.
f. For the ARANOTE study, the primary reasons for discontinuation of the study medication are listed. For the TITAN study, all reasons for discontinuation of the study medication are presented due to data availability.

ADT: androgen deprivation therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number of patients in the category; N: number of randomized patients; ND: no data; PSA: prostate-specific antigen; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients were largely balanced between the study arms in both ARANOTE and TITAN. In both studies, the patients were on average around 69 years old, the majority were of white family origin and were in good general health (ECOG-PS of 0 or 1). The patients predominantly had a Gleason score of ≥ 8 and high-volume disease.

There were differences between ARANOTE and TITAN in the proportion of patients with bone metastases, in the duration of ADT up to randomization and in the proportion of patients with prior docetaxel treatment. These aspects were taken into account in the examination of the similarity of the studies in Section I 3.3.

In both studies, fewer patients discontinued treatment in the intervention arm than in the control arm (ARANOTE: 46% versus 72%, TITAN: 34% versus 54%). In both study arms of both studies, the main reason for treatment discontinuation was disease progression. Overall, the proportion of patients who discontinued treatment was slightly higher in the ARANOTE study than in the TITAN study. This aspect was also taken into account in the examination of the similarity of the studies in Section I 3.3.

Information on the course of the study

Table 10 shows patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT[a] (multipage table)

Study Characteristic / Category	darolutamide + ADT vs. placebo + ADT		apalutamide + ADT vs. placebo + ADT	
	ARANOTE		TITAN	
	darolutamide + ADT	Placebo + ADT	apalutamide + ADT	Placebo + ADT
	N = 446	N = 223	N = 525	N = 527
Treatment duration [months]				
Median [min; max]	24.2 [0.0; 38.8]	17.3 [0.2; 36.7]	20.5 [ND; ND][a]	18.3 [ND; ND][a]
Mean (SD)	21.3 (9.2)	17.7 (9.3)	16.7 (8.0)	19.0 (7.8)
Observation period [months]				
Overall survival[b]				
Median [Q1; Q3]	25.3 [20.8; 29.3]	25.0 [18.9; 29.5]	20.4 [ND]	22.9 [ND]
Mean (SD)	23.7 (7.8)	22.9 (8.4)	ND	ND
Morbidity				
Symptomatic skeletal-related events	ND[c]	ND[c]	ND	ND
Worst pain (BPI-SF Question 3)				
Median [Q1; Q3]	22.5 [13.7; 27.4]	19.1 [10.0; 25.0]	20.2 [16.6; 24.0]	19.4 [14.8; 23.4]
Mean (SD)	20.5 (8.7)	17.8 (8.9)	ND	ND
Pain interference (BPI-SF Questions 9a–g)				
Median [Q1; Q3]	22.6 [13.7; 27.4]	19.1 [10.0; 25.0]	20.3 [16.6; 24.6]	19.7 [15.6; 24.0]
Mean (SD)	20.5 (8.7)	17.8 (8.9)	ND	ND
Health-related quality of life (FACT-P)				
Median [Q1; Q3]	22.8 [14.2; 27.6]	19.3 [11.2; 25.3]	ND	ND
Mean (SD)	20.9 (8.6)	18.1 (8.9)	ND	ND
Side effects				
Median [min; max]	24.2 [0.0; 38.8]	18.0 [0.2; 36.7]	ND	ND
Mean (SD)	21.6 (8.9)	18.3 (9.1)	ND	ND

a. For the TITAN study, only data on the median value [Q1; Q3] are available: intervention arm: 20.5 [14.9; 24.7]; control arm: 18.3 [10.3; 22.9].
b. The observation period for overall survival was defined in ARANOTE as the time to death or the last known date the patient was alive. For TITAN, no information is available on how the observation period was calculated.
c. Data are only available on the observation period up to the first event of the composite outcome; it is unclear how long patients were actually under observation for this outcome.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; max: maximum; min: minimum; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

In both studies, the median treatment duration was longer in the intervention arm than in the control arm (ARANOTE: 24.2 months versus 17.3 months; TITAN: 20.5 months versus 18.3 months). One reason contributing to this was that there were more progression events that led to treatment discontinuation in the respective control arms (see Table 9).

The median observation periods for the outcome overall survival and the patient-reported outcomes were comparable between the intervention and control arm of the ARANOTE study. The median observation periods of side effects were longer in the intervention arm than in the control arm of the ARANOTE study. No data were available regarding the observation period for the outcome of symptomatic skeletal-related events. For the TITAN study, data on median observation periods were only available for the outcomes overall survival and Brief Pain Inventory-Short Form (BPI-SF). These were comparable between the study arms.

It is noticeable for both studies that, despite the planned follow-up of the patient-reported outcomes of up to 12 months after the end of treatment, the actual observation period deviated only slightly from the treatment duration (for the intervention arm of the ARANOTE study it was even approx. 1.5 months shorter). A description of the similarity of treatment durations and observation periods between ARANOTE and TITAN can be found in Section I 3.3.

Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT[a] (multipage table)

Study **Drug**	**Patients with subsequent therapy n (%[a])**	
	darolutamide + ADT **N = 446**	**Placebo + ADT** **N = 223**
ARANOTE		
Patients with subsequent systemic therapy for prostate cancer	68 (15.2)	74 (33.2)
First subsequent therapy		
docetaxel	38 (8.5)	44 (19.7)
abiraterone, abiraterone acetate	19 (4.3)	11 (4.9)
enzalutamide	3 (0.7)	10 (4.5)
bicalutamide	4 (0.9)	3 (1.3)
apalutamide	3 (0.7)	0 (0)
flutamide	0 (0)	2 (0.9)
cabazitaxel	0 (0)	1 (0.4)
carboplatin	0 (0)	1 (0.4)
darolutamide	0 (0)	1 (0.4)
etoposide	0 (0)	1 (0.4)
radium-223 dichloride	1 (0.2)	0 (0)
rezvilutamide	0 (0)	1 (0.4)
Study **Drug class** **Drug**	**Patients with subsequent therapy n (%[a])**	
	apalutamide + ADT **N = 525**	**Placebo + ADT** **N = 527**
TITAN		
Patients with subsequent systemic therapy for prostate cancer	87 (16.6)	190 (36.1)
First subsequent therapy		
Hormonal therapy	44 (8.4)	98 (18.6)
abiraterone acetate + prednisone	21 (4.0)	45 (8.5)
bicalutamide	16 (3.0)	31 (5.9)
enzalutamide	3 (0.6)	17 (3.2)
Other[b]	4 (0.8)	5 (0.9)
Chemotherapy	35 (6.7)	73 (13.9)
docetaxel	29 (5.5)	67 (12.7)
cabazitaxel	1 (0.2)	2 (0.4)
Other[c]	5 (1.0)	4 (0.8)
Further therapies	8 (1.5)	19 (3.6)
radium-223	2 (0.4)	4 (0.8)
sipuleucel-T	2 (0.4)	5 (0.9)
Other[d]	4 (0.8)	10 (1.9)

Table 11: Information on subsequent antineoplastic therapies – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT[a] (multipage table)

Study Drug	Patients with subsequent therapy n (%[a])	
	darolutamide + ADT N = 446	Placebo + ADT N = 223
a. Percentages refer to all patients in the respective arms (TITAN: Institute's calculation). b. Diethylstilbestrol, flutamide, cyproterone. c. Etoposide, paclitaxel, estramustine, carboplatin and cisplatin. d. Zoledronic acid, clodronate, prednisolone, prednisone. ADT: androgen deprivation therapy; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial		

In each of the studies ARANOTE and TITAN, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The proportion of patients in the ARANOTE study who received at least one subsequent therapy was 15.2% in the intervention arm and 33.2% in the control arm. Assuming that subsequent therapy was only indicated for patients with radiological disease progression (99 patients in the intervention arm versus 80 patients in the control arm), 68.7% versus 92.5% of these patients received subsequent therapy. In the TITAN study, 16.6% of patients in the intervention arm versus 36.1% in the control arm received at least one subsequent therapy. Referring to patients with an rPFS event (134 versus 231), 64.9% versus 82.3% received subsequent therapy. However, no data were available on how many rPFS events were attributable to deaths. It was therefore unclear for how many of the patients in the study subsequent therapy was indicated.

After radiological disease progression, patients in this therapeutic indication are in the stage of metastatic castration-resistant cancer, according to the S3 guideline on prostate cancer, for which systemic therapy is recommended [23]. It therefore remained unclear why a relevant proportion of patients in both ARANOTE and TITAN, particularly in the intervention arms, did not receive subsequent therapy. A possible reason in both studies was the option for patients to continue treatment with the study medication beyond progression, as permitted by the study protocol. However, there was no information on how many patients received such continued treatment and for how long.

The most frequently used first subsequent therapies in the ARANOTE study were docetaxel and abiraterone (acetate), and in the control arm additionally enzalutamide. In the TITAN study, patients most frequently received docetaxel, abiraterone acetate and bicalutamide, and in the control arm additionally enzalutamide, as the first subsequent therapy. These subsequent therapies mostly corresponded to the recommendations of the S3 guideline on prostate cancer [23] and were comparable between the studies. An exception to this was subsequent treatment with bicalutamide, which 11.9% of patients in the intervention arm and

13.4% of patients in the control arm (referring to patients with an rPFS event) received in the TITAN study and which did not comply with the recommendations of the S3 guideline [23]. Since the proportions of patients with subsequent bicalutamide therapy did not differ between the study arms and were low in relation to the number of randomized patients, this had no consequences for the benefit assessment.

With regard to the transferability of the study results to the current health care context, it should be noted that in both ARANOTE and TITAN, none of the patients received olaparib treatment as their first subsequent therapy, which according to the S3 guideline should be offered in the presence of a breast cancer-associated gene (BRCA)1/2 mutation and progression after prior therapy with an androgen receptor signalling pathway inhibitor [23]. It was unclear how many patients in ARANOTE and TITAN had a BRCA1/2 mutation, and due to the time period in which the studies were conducted (start of TITAN: 2015; start of ARANOTE: 2021; marketing authorization of olaparib: 2020), it is unlikely, especially for the TITAN study, that a corresponding test was regularly conducted before initiating subsequent therapy. It can be inferred from the S3 guideline that BRCA1/2 mutations are present in around 10% of patients with metastatic castration-resistant prostate cancer [23], so that olaparib treatment might also have been indicated for a small proportion of the study populations in ARANOTE and TITAN. However, due to this expected low proportion, there was no consequence for the benefit assessment.

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
darolutamide + ADT vs. placebo + ADT							
ARANOTE	Yes	Yes	Yes	Yes	Yes	Yes	Low
apalutamide + ADT vs. placebo + ADT							
TITAN	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

Transferability of the study results to the German health care context

ARANOTE

From the company's point of view, it could be assumed that the results of the ARANOTE study were transferable to the German health care context. According to the company, most of the patients (intervention arm: 42%, control arm: 40%) were enrolled in Australia, Canada, New Zealand, South Africa or Europe; in each case, 56% of the patients in both study arms were of white family origin; and the median patient age of 70 years was comparable to the median patient age at the onset of prostate cancer in Germany (71 years) [24].

TITAN

The company also considered the results of the TITAN study to be transferable to the German health care context. According to the company, the majority of the patients included were of white family origin (intervention arm: 67%, control arm: 69%); and the median patient age of 69 years in the intervention arm and 68 years in the control arm was comparable to the median patient age at the onset of prostate cancer in Germany (71 years) [24].

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

I 3.3 Similarity of the studies for the indirect comparison

Similarity is a key requirement for the consideration of studies in an adjusted indirect comparison via a common comparator. ARANOTE and TITAN had a similar overall study design. The patient populations were also sufficiently similar. This is described below.

Similarity of study conduct

Study design

The 2 studies ARANOTE and TITAN were double-blind RCTs including adult patients with metastatic hormone-sensitive prostate cancer. In contrast to the ARANOTE study, however, the TITAN study only included patients who had at least bone metastases. Furthermore, patients in the TITAN study had to be in a good general condition corresponding to an ECOG PS ≤ 1, whereas in the ARANOTE study an ECOG PS of 2 was also permitted. In contrast to the ARANOTE study, prior therapy with docetaxel was also permitted in the TITAN study. The maximum duration of prior ADT before randomization was 12 weeks for ARANOTE and 6 months for TITAN.

Moreover, the periods of study conduct differed. The TITAN study started in 2015, while the ARANOTE study did not start until 2021.

However, these differences in study design had no impact on the characteristics of the patient populations that would call into question the similarity of ARANOTE and TITAN. This is described below, in particular in the section on the similarity of the patient population.

Planned duration of follow-up

For the majority of the relevant outcomes of ARANOTE and TITAN, the planned durations of follow-up were comparable (see Table 8). There was a difference in the recording of the outcome of symptomatic skeletal-related events. For this outcome, a follow-up of up to 12 months after the last dose of study medication was planned in the ARANOTE study, but until the end of the study in the TITAN study. However, this had no consequences for this benefit assessment, as there were no suitable data for the indirect comparison for the outcome symptomatic skeletal-related events regardless of this aspect (see Section I 4.1).

Subsequent therapies

The information on subsequent therapies from the ARANOTE and TITAN studies presented in Table 11 corresponds in the majority of cases to the recommendations of the S3 guideline on prostate cancer [23] and was assessed as sufficiently similar overall. The difference with regard to subsequent bicalutamide therapy was of a magnitude that was not expected to jeopardize the similarity of ARANOTE and TITAN (see also Section I 3.2 on subsequent therapies).

Similarity of the patient population

Patient characteristics

The demographic and clinical characteristics of the included patients, such as age, family origin and disease volume, were sufficiently comparable between the studies (see Table 9).

There were differences in the patient characteristics with regard to the patients' ECOG PS. In the ARANOTE study, around half of the patients had an ECOG PS of 0, while in the TITAN study the figure was slightly higher (around two-thirds of patients). However, since most patients in both studies were in good general condition overall (ECOG PS 0 or 1), it was assumed that the study populations were sufficiently similar with regard to this aspect.

Another difference was seen in the proportion of patients with bone metastases at baseline. While 100% of patients in the TITAN study had bone metastases due to the study design, the proportion in the ARANOTE study was only 77% (see Table 9). However, the similarity of the patient populations in ARANOTE and TITAN was not fundamentally called into question by this difference, also due to the sufficient comparability in disease volume (high versus low) of the patients between the studies. Nevertheless, it would be useful to examine the effects of this difference on the results of the indirect comparison, for example by means of corresponding sensitivity analyses exclusively for patients with bone metastases.

Prior treatment

Prior treatment with docetaxel

While no patients with prior docetaxel treatment were included in the ARANOTE study due to the study design, around 11% of patients in the TITAN study had received prior docetaxel treatment. However, due to this low proportion, it was assumed that the study populations in ARANOTE and TITAN were sufficiently similar in this respect.

Prior treatment with ADT

Another difference between the studies was seen in the duration of prior treatment with ADT. The patients in the ARANOTE study had received prior treatment with ADT for a median time period of around 1 month. In the TITAN study, this time period was about 1.8 months (see Table 9). According to the S3 guideline, patients with metastatic hormone-sensitive prostate cancer should be offered additional treatment with apalutamide, enzalutamide or darolutamide no later than within 3 months of initiating ADT [23]. The median time to starting study treatment was therefore within the recommended period in both studies. However, in 25% of the patients in the TITAN study treatment was only initiated after 3.5 months; whereas in the ARANOTE study, all patients started the treatment within 3 months (see Table 9). However, as ADT is used permanently, this deviation in the duration of prior treatment was not expected to have a significant impact on the similarity of the patient populations, when compared with the total treatment duration of the 2 studies (see Table 10).

Similarity of the common comparator

The treatment in the common comparator arm was placebo + ADT in both studies. With the exception of the difference already described in the duration of prior treatment with ADT, treatment was comparable in both studies, so that sufficient similarity was assumed with regard to the common comparator placebo + ADT.

Treatment duration

The median treatment durations of the control arms of ARANOTE and TITAN were comparable (17.3 months versus 18.3 months) (see Table 10). It was therefore assumed that the treatment durations were sufficiently similar.

Frequency of treatment discontinuation

Differences in the proportion of patients who discontinued the study treatment were particularly evident between the control arms of ARANOTE and TITAN (72% versus 54%; see Table 9). This was mainly due to the somewhat more frequent treatment discontinuations in the control arm of the ARANOTE study due to withdrawal of consent by the patient and due to adverse events (AEs). The reasons for these differences were unclear. However, due to the blinded study design in particular, it was not assumed that this called into question the similarity of the studies.

Summary of the similarity of the studies

Overall, there were some differences in the study and patient characteristics between ARANOTE and TITAN, but none of them fundamentally called into question their similarity for conducting an adjusted indirect comparison via the common comparator placebo + ADT.

This concurred with the company's assessment, which also assumed that the studies were sufficiently similar to conduct an adjusted indirect comparison.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Pain, recorded using the BPI-SF
    - Worst pain (Item 3)
    - Pain interference (Item 9 a–g)
  - Symptomatic skeletal-related events
  - Fatigue, recorded using the Brief Fatigue Inventory (BFI)
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the Functional Assessment of Cancer Therapy-Prostate (FACT-P)
- Side effects
  - Serious AEs (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Fall (Preferred Term [PT], AEs)
  - Other specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT

Comparison / Study	Outcomes											
	Overall survival	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a–g)	Symptomatic skeletal-related events[a]	Fatigue (BFI)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Fall (PT, AEs)	Other specific AEs
darolutamide + ADT vs. placebo + ADT												
ARANOTE	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	No[d]
apalutamide + ADT vs. placebo + ADT												
TITAN	Yes	No[e]	Yes	No[e]	No[f]	No[f]	No[e]	Yes	Yes	Yes	Yes	No[d]
Indirect comparison feasible	Yes	No[g]	No[h]	No[g]	No[g]	No[g]	No[g]	No[h]	No[h]	No[h]	No[h]	No[d]

a. Defined in ARANOTE as: EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression or tumour-related orthopaedic surgical intervention; in TITAN defined as: radiation to bone, occurrence of a new symptomatic pathological fracture, spinal cord compression or surgery to bone.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Outcome not recorded.
d. No further specific AEs were selected based on the AEs that occurred in the relevant study, as the requirements for the certainty of results for conducting an unadjusted indirect comparison were not met for any of the AEs (see Section I 4.2).
e. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
f. Outcome recorded in the TITAN study, but no data are available in Module 4.
g. Indirect comparison not feasible because no (suitable) data are available for at least one side of the indirect comparison.
h. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section I 4.2).

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EBRT: external beam radiotherapy; FACT-P: Functional Assessment of Cancer Therapy-Prostate; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on the included outcomes

Worst pain (BPI-SF Item 3)

For the outcome of worst pain (recorded using Item 3 of the BPI-SF), the company presented responder analyses for the indirect comparison on the time to confirmed deterioration as well

as on confirmed improvement, each by at least 2 points. According to the company, no results were available for the operationalization of a first-time deterioration, which is why it was not possible to calculate the adjusted indirect comparison.

In the given situation, the responder analyses presented by the company were not suitable for the benefit assessment. In ARANOTE and TITAN, the median observation periods in the intervention and control arms were initially sufficiently comparable (see Table 10). Over the course of the ARANOTE study, however, there was a continuous decrease in the proportion of completed questionnaires, which differed between the study arms and could not be explained solely by the patients who died during the observation period. For example, at around Month 18, the response rate in the control arm was more than 20 percentage points lower than in the intervention arm (Institute's calculations). Therefore, it could not be assumed with certainty that the observation periods were sufficiently equal over the course of the studies. In such a situation, the G-BA requires the presentation of responder analyses on the time to first deterioration [25]. The indirect comparison of the time to confirmed deterioration presented by the company instead did not meet the requirements of the G-BA and was therefore not used for the benefit assessment. Analyses on the time to first deterioration were presented in the company's dossier for the ARANOTE study, but not for the TITAN study. However, due to the decrease in questionnaire return rates over the course of the study, which differed between the study arms, there would not be sufficient certainty of results for conducting an adjusted indirect comparison for this operationalization either (see Section I 4.2).

Overall, there were therefore no suitable data for an indirect comparison of ARANOTE and TITAN for the outcome worst pain.

Symptomatic skeletal-related events

The composite outcome of symptomatic skeletal-related events comprised the following individual components:

- External beam radiotherapy to relieve skeletal symptoms (ARANOTE) or radiation to bone (TITAN)
- New symptomatic pathologic bone fracture (ARANOTE) or occurrence of a new symptomatic pathological fracture (TITAN)
- Occurrence of spinal cord compression (ARANOTE and TITAN)
- Tumour-related orthopaedic surgical intervention (ARANOTE) or surgery to bone (TITAN)

In principle, the outcome symptomatic skeletal-related events was relevant for the benefit assessment. However, the company's dossier lacked information on the occurrence of the individual subcomponents in the TITAN study. This information would have been necessary to

assess the results of this outcome, for example to draw conclusions about the direction of effect of the subcomponents. Thus, no suitable data for the benefit assessment were available from the TITAN study; the indirect comparison presented by the company was therefore not used.

Health-related quality of life, recorded with the FACT-P

For the outcome of health-related quality of life (recorded using the FACT-P), the company presented in Module 4 responder analyses for the indirect comparison on the time to first deterioration as well as on first improvement, each by at least 10 points.

The responder analyses presented by the company were unsuitable for this benefit assessment. According to the dossier template, responder analyses with a response threshold of at least 15% of the scale range of the survey instrument used should be presented for the benefit assessment. The 15% response threshold of the FACT-P total score (scale range of 156 points) is 23.4 points. In the company's dossier, results on the time to deterioration by 23.4 points were only available for the ARANOTE study, but not for the TITAN study. The indirect comparison of the time to deterioration by 10 points presented by the company instead did not correspond to the requirements of the dossier template and was therefore not used.

Instead of responder analyses, the dossier template also provides the option of presenting analyses of continuous data. The study protocols of both ARANOTE and TITAN prespecified analyses of change from baseline for the outcome FACT-P. However, the company's dossier did not present results for either of the 2 studies and accordingly no indirect comparison for this operationalization.

Overall, no suitable data in the outcome category of health-related quality of life were therefore available for the benefit assessment.

I 4.2 **Risk of bias**

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT

Study	Study level	Outcomes											
		Overall survival	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a–g)	Symptomatic skeletal-related events[a]	Fatigue (BFI)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Fall (PT, AEs)	Other specific AEs
darolutamide + ADT vs. placebo + ADT													
ARANOTE	L	L	H[c]	H[c]	H[d]	–[e]	–[e]	H[c]	H[f]	H[f]	L	H[f]	–
apalutamide + ADT vs. placebo + ADT													
TITAN	L	L	–[g]	L	–[g]	–[h]	–[h]	–[g]	H[f]	H[f]	L	H[f]	–

a. Defined in ARANOTE as: EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression or tumour-related orthopaedic surgical intervention; in TITAN defined as: radiation to bone, new symptomatic pathological fracture, spinal cord compression or surgery to bone.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Decrease in questionnaire return rates over the course of the study, which differed between study arms.
d. Unknown observation periods and early onset of censoring with low event frequency.
e. Outcome not recorded.
f. Incomplete observations for potentially informative reasons with different follow-up observations.
g. No suitable data available; for reasoning, see Section I 4.1 of this dossier assessment.
h. Risk of bias not assessed, as no data on this outcome are available in the company's dossier.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EBRT: external beam radiotherapy; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

ARANOTE

For the results of the outcome overall survival, the risk of bias was assessed as low.

The results on morbidity and health-related quality of life, recorded via the outcomes worst pain (BPI-SF Item 3), pain interference (BPI-SF Item 9a–9g) and FACT-P, each have a high risk of bias. This was due to a decrease in questionnaire return rates over the course of the study, which differed between study arms.

For the outcome of symptomatic skeletal-related events, the risk of bias was also assessed as high due to unknown observation periods and censoring that began to a relevant extent early in the course of the study. For example, the Kaplan-Meier curves presented in Module 4 showed that by Month 6, around 10% of patients were no longer at risk, with a very low frequency of events up to this timepoint. The reasons for this were largely unclear.

The risk of bias for the outcomes in the side effects category, with the exception of the outcome of discontinuation due to AEs, was also rated as high. This was due to the high number of incompletely observed patients, which differed between the study arms. These resulted from the fact that the recording of side effects was linked to the end of study treatment (see Table 8), and that 46% of patients in the intervention versus 72% in the control arm discontinued treatment (see Table 9).

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

The risk of bias was not assessed for the other included outcomes, as no (suitable) analyses for the benefit assessment were available.

TITAN

For the results on the outcomes of overall survival and pain interference (BPI-SF Item 9a–9g), the risk of bias was assessed as low.

For the results in the side effects category, with the exception of the outcome of discontinuation due to AEs, the risk of bias was assessed as high due to potentially high proportions of incompletely observed patients that differed between the study arms. These resulted from the fact that the recording of side effects was linked to the end of study treatment (see Table 8), and that 34% of patients in the intervention versus 54% in the control arm discontinued treatment (see Table 9).

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

The risk of bias was not assessed for the other included outcomes, as no (suitable) analyses for the benefit assessment were available.

Consequences for the indirect comparison

If only one study is available on one side of an indirect comparison and results of individual outcomes of this study have a high risk of bias, the certainty of results required to conduct an adjusted indirect comparison is insufficient.

In summary, data with sufficient certainty of results in both studies, which would allow an informative adjusted indirect comparison to be conducted, were therefore only available for the outcome overall survival.

I 4.3 Results

Table 15 summarizes the results of the comparison of darolutamide + ADT versus apalutamide + ADT in adult men with metastatic hormone-sensitive prostate cancer. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Outcome category Outcome Comparison Study	darolutamide + ADT / apalutamide + ADT N	 Median time to event in months [95% CI] Patients with event n (%)	placebo + ADT N	 Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value
Mortality					
Overall survival					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	446	NA 103 (23.1)	223	NA [33.8; NC] 60 (26.9)	0.81 [0.59; 1.12]; 0.201[a]
apalutamide + ADT vs. placebo + ADT					
TITAN	525	NA 83 (15.8)	527	NA 117 (22.2)	0.67 [0.51; 0.89]; 0.005[b]
Indirect comparison using common comparators[c]:					
darolutamide + ADT vs. apalutamide + ADT					1.21 [0.79; 1.86]; 0.375
Morbidity					
Worst pain (BPI-SF Item 3)	No suitable data for the indirect comparison[d]				
Pain interference (BPI-SF Item 9a–g – time to first deterioration[e])					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	446	NA [33.0; NC] 132 (29.6)	223	26.9 [17.5; NC] 91 (40.8)	0.64 [0.49; 0.83]; < 0.001[a]
apalutamide + ADT vs. placebo + ADT					
TITAN	525	NA 91 (17.3)	527	NA 106 (20.1)	0.84 [0.63;1.11]; 0.213[f]
Indirect comparison using common comparators[c]:					
darolutamide + ADT vs. apalutamide + ADT					–[g]
Symptomatic skeletal-related events[h]	No suitable data for the indirect comparison[d]				
Fatigue (BFI)	No suitable data for the indirect comparison[d]				
Health status (EQ-5D VAS)	No suitable data for the indirect comparison[d]				
Health-related quality of life					
FACT-P	No suitable data for the indirect comparison[d]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Outcome category **Outcome**	**darolutamide + ADT / apalutamide + ADT**		**placebo + ADT**		**Group difference**
Comparison **Study**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
Side effects					
AEs					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	445	3.7 [2.9; 5.0] 405 (91.0)	221	3.3 [2.8; 5.2] 199 (90.0)	–
apalutamide + ADT vs. placebo + ADT					
TITAN	524	1.0 [1.0; 1.3] 507 (96.8)	527	1.7 [1.4; 1.9] 509 (96.6)	–
SAEs					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	445	NA 105 (23.6)	221	NA 52 (23.5)	0.90 [0.64; 1.25]; 0.524[i]
apalutamide + ADT vs. placebo + ADT					
TITAN	524	NA 104 (19.8)	527	NA 107 (20.3)	0.91 [0.70;1.20]; 0.516[f]
Indirect comparison using common comparators[c]:					
darolutamide + ADT vs. apalutamide + ADT					[j]
Severe AEs[k]					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	445	NA 158 (35.5)	221	NA [26.6; NC] 79 (35.7)	0.90 [0.69; 1.18]; 0.449[i]
apalutamide + ADT vs. placebo + ADT					
TITAN	524	NA [23.5; NC] 223 (42.6)	527	NA [20.3; NC] 222 (42.1)	0.99 [0.83;1.20]; 0.961[f]
Indirect comparison using common comparators[c]:					
darolutamide + ADT vs. apalutamide + ADT					[j]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Outcome category Outcome	darolutamide + ADT / apalutamide + ADT		placebo + ADT		Group difference
Comparison Study	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Discontinuation due to AEs					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	445	NA 27 (6.1)	221	NA 20 (9.0)	0.58 [0.32; 1.03]; 0.060[i]
apalutamide + ADT vs. placebo + ADT					
TITAN	524	NA 42 (8.0)	527	NA 28 (5.3)	1.41 [0.87;2.27]; 0.162[f]
Indirect comparison using common comparators[c]:					
darolutamide + ADT vs. apalutamide + ADT					–[i]
Fall (PT, AEs)					
darolutamide + ADT vs. placebo + ADT					
ARANOTE	445	NA 5 (1.1)	221	NA 2 (0.9)	1.11 [0.21; 5.71]; 0.904[i]
apalutamide + ADT vs. placebo + ADT					
TITAN	524	NA 39 (7.4)	527	NA 37 (7.0)	0.90 [0.57;1.42]; 0.658[f]
Indirect comparison using common comparators[c]:					
darolutamide + ADT vs. apalutamide + ADT					–[g]

a. HR and 95% CI from stratified Cox model, p-value from log-rank test, each stratified according to the presence of visceral metastases and prior local therapy from the IWRS.
b. HR and 95% CI from stratified Cox model, p-value from log-rank test, each stratified by Gleason score at diagnosis (≤ 7 months vs. > 7 months), geographical region (North America / EU vs. other countries) and prior docetaxel use (yes vs. no).
c. Indirect comparison according to Bucher [3].
d. Indirect comparison not feasible because no (suitable) data are available for at least one side of the indirect comparison (see Section I 4.1 for reasons).
e. An increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10).
f. HR, 95% CI and p-value from Cox model, stratified by Gleason score at diagnosis (≤ 7 months vs. > 7 months), geographical region (North America / EU vs. other countries) and prior docetaxel use (yes vs. no).
g. The requirement for the certainty of results to perform an adjusted indirect comparison is not met.
h. Defined in ARANOTE as: EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression or tumour-related orthopaedic surgical intervention; in TITAN defined as: radiation to bone, new symptomatic pathological fracture, spinal cord compression or surgery to bone.
i. HR and CI from unstratified Cox model; p-value from unstratified log-rank test.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Outcome category Outcome	darolutamide + ADT / apalutamide + ADT		placebo + ADT		Group difference
Comparison Study	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value

j. The requirement for the certainty of results to perform an adjusted indirect comparison is not met. The effect estimates are presented as supplementary information in I Appendix D of the full dossier assessment.
k. Severe AEs are operationalized as CTCAE grade ≥ 3.

ADT: androgen deprivation therapy; AE: adverse event; BFI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EBRT: external beam radiotherapy; EU: European Union; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; IWRS: interactive web response system; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PT: Preferred term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

There was one RCT on each side of the available adjusted indirect comparison. Consequently, there was no need to assess homogeneity. As there was no study of direct comparison of darolutamide + ADT versus the ACT, it was impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, no more than hints, e.g. of an added benefit, could be derived on the basis of the data available from the adjusted indirect comparison.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between darolutamide + ADT versus apalutamide + ADT for the outcome overall survival. There is no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Morbidity

Worst pain, symptomatic skeletal-related events, fatigue, health status

There were no suitable data for the outcomes in the category of worst pain (recorded using the BPI-SF Item 3), symptomatic skeletal-related events, fatigue (recorded using the BFI) and health status (recorded using EQ-5D VAS). In each case, there is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Pain interference

Due to insufficient certainty of results in the ARANOTE study, it was not possible to conduct an indirect comparison for the outcome of pain interference (recorded using the BPI-SF Item 9a–9g). There is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Health-related quality of life

No suitable data were available for the outcome of health-related quality of life, recorded using the FACT-P. There is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

Side effects

Due to the insufficient certainty of results in ARANOTE and TITAN, it was not possible to conduct an indirect comparison for the outcomes in the side effects category. In each case, there is therefore no hint of an added benefit of darolutamide + ADT in comparison with apalutamide + ADT; an added benefit is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (< 65 years versus 65–74 years versus ≥ 75 years)
- High-volume prostate cancer (yes versus no)

The characteristic of sex was disregarded because the therapeutic indication in question only includes men.

The subgroup characteristic of high-volume prostate cancer was predefined in ARANOTE and TITAN. The subgroup characteristic of age, with the cut-off points shown above, was predefined exclusively for the TITAN study. For both characteristics, subgroup analyses for the indirect comparison of ARANOTE and TITAN were available in Module 4.

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

Applying the methods described above, no effect modifications relevant to the benefit assessment were shown for the characteristics of age and high-volume prostate cancer.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 16).

Table 16: Extent of added benefit at outcome level: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Outcome category **Outcome**	**darolutamide + ADT vs. apalutamide + ADT** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 1.21 [0.79; 1.86]; p = 0.375	Lesser benefit/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF Item 3)	No suitable data[c]	Lesser benefit/added benefit not proven
Pain interference (BPI-SF Item 9a–g)	No suitable data[d]	Lesser benefit/added benefit not proven
Symptomatic skeletal-related events	No suitable data[c]	Lesser benefit/added benefit not proven
Fatigue (BFI)	No suitable data[c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-P	No suitable data[c]	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: darolutamide + ADT vs. apalutamide + ADT (multipage table)

Outcome category **Outcome**	**darolutamide + ADT vs. apalutamide + ADT** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	No suitable data[d]	Lesser benefit/added benefit not proven
Severe AEs[e]	No suitable data[d]	Lesser benefit/added benefit not proven
Discontinuation due to AEs	No suitable data[d]	Lesser benefit/added benefit not proven
Fall (PT, AEs)	No suitable data[d]	Lesser benefit/added benefit not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Indirect comparison not feasible because no (suitable) results are available for at least one side of the indirect comparison (see Section I 4.1 for reasons).
d. The requirement for the certainty of results to perform an adjusted indirect comparison is not met.
e. Operationalized as CTCAE ≥ 3.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval, CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 **Overall conclusion on added benefit**

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

Table 17: Positive and negative effects from the assessment of darolutamide + ADT in comparison with apalutamide + ADT

Positive effects	**Negative effects**
–	–
No data suitable for the indirect comparison are available for the outcomes of morbidity, health-related quality of life and side effects.	
ADT: androgen deprivation therapy	

Overall, based on the adjusted indirect comparison using the common comparator of placebo + ADT, there are neither positive nor negative effects of darolutamide + ADT in

comparison with apalutamide + ADT. However, it should be noted that usable results with sufficient certainty of results for an indirect comparison were only available for the outcome overall survival.

In summary, there is no hint of an added benefit of darolutamide + ADT versus apalutamide + ADT for adult men with metastatic hormone-sensitive prostate cancer.

The result of the assessment of the added benefit of darolutamide + ADT in comparison with the ACT is summarized in Table 18.

Table 18: Darolutamide + ADT – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adult men with metastatic hormone-sensitive prostate cancer	▪ Conventional ADT[c] in combination with apalutamide or ▪ Conventional ADT[c] in combination with enzalutamide or ▪ Conventional ADT[c] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk prostate cancer) or ▪ Conventional ADT[c] in combination with darolutamide and docetaxel or	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, in the present therapeutic indication, it is assumed that combination therapy – additional therapy to conventional ADT – is usually an option for the patients, taking into account any comorbidities and the general condition.
c. In the context of the present therapeutic indication, conventional ADT refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists.

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

The assessment described above deviates from that of the company, which derived a hint of a considerable added benefit.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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