IQWiG Reports – Commission No. A20-36

Apalutamide (prostate cancer) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Apalutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 29 June 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
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)
MFS	metastasis-free survival
nmCRPC	nonmetastatic castration-resistant prostate cancer
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	system organ class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug apalutamide. 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 31 March 2020.

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

In accordance with the justification paper on the decision dated 1 August 2019, a limit was placed on the validity period after data on overall survival available for the assessment from the SPARTAN study were of little informative value at the data cut-off used given that few events had occurred. For benefit reassessment, a study data cut-off of 1 December 2019 was to be used.

Research question

The aim of this report is to assess the added benefit of apalutamide in comparison with the appropriate comparator therapy (ACT) of watchful waiting, each while maintaining ongoing conventional androgen deprivation therapy (ADT) in adult men with nonmetastatic castration-resistant prostate cancer (nmCRPC) who have a high risk of developing metastases.

Table 2: Research question of the benefit assessment of apalutamide

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

The company followed the G-BA's specification 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. RCTs were used for the derivation of added benefit.

Results

The benefit assessment includes the SPARTAN study and assesses the data cut-off date of 1 December 2019.

Study design

The SPARTAN study is a randomized, double-blind, multicentre study which compares apalutamide in combination with ADT with treatment with ADT and the additional administration of placebo. Included were adult men with high-risk nmCRPC. Included patients had to have either undergone surgical castration or had to continue drug-based ADT using GnRH (gonadotropin-releasing hormone) analogues in addition to the study drug.

A total of 1207 patients were randomized in a 2:1 ratio, 806 into the intervention arm of apalutamide + ADT and 401 patients into the control arm of placebo + ADT. Apalutamide treatment was implemented without relevant deviations from the specifications of the Summary of Product Characteristics (SPC).

The primary outcome of the study was metastasis-free survival (MFS). Patient-relevant secondary outcomes were overall survival, symptomatic progression, health status, health-related quality of life, and adverse events (AEs).

The study is still ongoing. Following the primary analysis, which was based on the 1st data cut-off (19 May 2017), the study was unblinded (22 July 2017). Patients who were still being treated in the control arm were given the option to switch to apalutamide treatment while maintaining ongoing ADT.

Risk of bias

The risk of bias at study level is assessed as low.

The risk of bias of the outcome of overall survival is rated as high because a relevant number of 76 patients (19%) switched treatment after the study was unblinded. All further outcomes are also deemed potentially highly biased.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found between treatment arms in favour of apalutamide + ADT in comparison with placebo + ADT. This results in a hint of an added benefit in favour of apalutamide + ADT in comparison with watchful waiting + ADT.

Morbidity

Symptomatic progression

The outcome of symptomatic progression is a combined outcome which includes the following events:

- development of a skeletal-related event (pathological fractures, compression of the spinal cord, or requirement of a surgical intervention or radiation therapy of the bone)
- pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy as well as
- development of clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy.

For the outcome of symptomatic progression, a statistically significant difference between treatment arms was found in favour of apalutamide + ADT in comparison with placebo + ADT. Considered together with the results from the 1st data cut-off from 19 May 2017, high certainty of results is assumed for this outcome despite the high risk of bias. This results in an indication of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT.

However, the chosen operationalization of this outcome is unsuitable for comprehensively recording the events of pain progression or progression of other disease-related symptoms. For this reason, the extent of added benefit is not quantifiable for the outcome of symptomatic progression.

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

No usable data are available for the outcome of health status as measured using EQ-5D VAS. Consequently, there is no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

Health-related quality of life

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

For health-related quality of life as measured using the FACT-P, no statistically significant difference between treatment arms was found. Consequently, there is no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

AEs

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

For each of the outcomes of SAEs, severe AEs (CTCAE ≥ grade 3), and discontinuation due to AEs, no statistically significant difference between treatment arms was found. For each of these outcomes, this results in no hint of greater or lesser harm of apalutamide + ADT in comparison with watchful waiting + ADT; therefore, there is no proof of greater or lesser harm.

Specific AEs

Arthralgia (preferred term [PT], AEs), nervous system disorders (system organ class [SOC], AEs), hypothyroidism (PT, AEs), infections and infestations (SOC, SAEs), injury, poisoning, and procedural complications (SOC, SAEs)

For each of the outcomes of arthralgia (PT, AEs), nervous system disorders (SOC, AEs), hypothyroidism (PT, AEs), infections and infestations (SOC, SAEs), and injury, poisoning, and procedural complications (SOC, SAEs), a statistically significant difference was found to the disadvantage of apalutamide + ADT in comparison with placebo + ADT. For each of these outcomes, this results in a hint of greater harm of apalutamide + ADT in comparison with watchful waiting + ADT.

Skin and subcutaneous tissue disorders, severe AEs (SOC, severe AEs [CTCAE grade ≥ 3]):

For the outcome of skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was found to the disadvantage of apalutamide + ADT in comparison with placebo + ADT. Despite the high risk of bias, a high certainty of results is assumed due to the effect size. This results in an indication of greater harm of apalutamide + ADT in comparison with watchful waiting + ADT.

Severe AEs (CTCAE grade ≥ 3): Renal and urinary disorders (SOC)

For the outcome of renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was found in favour of apalutamide + ADT in comparison with placebo + ADT. This results in a hint of lesser harm of apalutamide + ADT in comparison with watchful waiting + ADT. Overall, however, it is questionable whether the effect is actually to be attributed to the outcome category of AEs or whether it rather reflects the disease symptoms. The events occurring under the SOC comprised typical locoregional symptoms of prostate cancer, e.g. urinary retention and hydronephrosis.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug apalutamide in comparison with the ACT are assessed as follows:

In terms of favourable effects, the aggregate view of results reveals an indication of non-quantifiable added benefit in the morbidity outcome category as well as a hint of considerable added benefit for the outcome of overall survival. Moreover, there is 1 hint of another

[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].

favourable effect in the category of serious/severe AEs. However, it is questionable whether the favourable effect on the outcome of renal and urinary disorders is actually to be attributed to the outcome category of AEs or whether it rather reflects the symptoms of the disease. On the basis of the available information, an unequivocal differentiation is impossible.

The favourable effects are offset by 1 indication and several hints of unfavourable effects in the outcome category of AEs, some of major and some of considerable extent. Overall, however, the unfavourable effects do not completely offset the favourable effects.

All things considered, for patients with nmCRPC and a high risk of developing metastases, there is an indication of considerable added benefit of apalutamide + ADT in comparison with the ACT of watchful waiting + ADT.

Table 3 presents a summary of the probability and extent of added benefit of apalutamide.

Table 3: Apalutamide – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult men with nonmetastatic castration-resistant prostate cancer who have a high risk of developing metastases	Watchful waiting while maintaining ongoing conventional ADT[b]	Indication of considerable added benefit
a. Presentation of the respective ACT specified by the G-BA. b. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone		

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

2.2 Research question

The aim of this report is to assess the added benefit of apalutamide in comparison with the ACT of watchful waiting, each while maintaining ongoing conventional ADT, in adult men with nmCRPC who have a high risk of developing metastases.

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

Table 4: Research questions of the benefit assessment of apalutamide

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

The company followed the G-BA's specification 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. Randomized controlled trials (RCTs) were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- Study list on apalutamide (as of 27 March 2020)
- Bibliographic literature search on apalutamide (most recent search on 9 March 2020)
- Search in trial registries / study results databases on apalutamide (most recent search on 18 March 2020)
- Search on the G-BA website on apalutamide (most recent search on 18 March 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on apalutamide (most recent search on 7 April 2020)

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

Table 5: Study pool – RCT, direct comparison: apalutamide + ADT versus watchful waiting + ADT

Study	Study category			Available sources		
	Approval study for the drug to be assessed (Yes/No)	Sponsored study[a] (Yes/No)	Third-party study (Yes/No)	Clinical study report (Yes/No [reference])	Registry entries[b] (Yes/No [reference])	Publication and other sources[c] (Yes/No [reference])
SPARTAN	Yes	Yes	No	No[d]	Yes [3-8]	Yes [9-17]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website.
d. Due to working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data provided in Module 5 of the company's dossier.

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

The study pool is consistent with that of the company. The SPARTAN study was already presented and evaluated in the previous benefit assessment of apalutamide. In the justification paper of the initial assessment, the G-BA imposed validity time limits and required another data cut-off on 1 December 2019 [18]. The present benefit assessment is based on the results of this data cut-off.

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
SPARTAN	RCT, double-blind, parallel	Adult patients with high-risk (PSADT ≤ 10 months), nonmetastatic, castration-resistant[b] prostate cancer	Apalutamide + ADT (N = 806) Placebo + ADT (N = 401)	Screening: up to 35 days Treatment: until documented radiographic progression (development of distant metastases), withdrawal of informed consent, or unacceptable toxicity Observation[c]: outcome-specific, at most until death, lost to follow-up, or withdrawal of informed consent	234 centres in 26 countries in Asia, Australia, Canada, Europe, New Zealand, Russia, and the United States 9/2013–ongoing 1st data cut-off: 19/05/2017 (prespecified analysis) 2nd data cut-off: 01/02/2019 (post hoc) 3rd data cut-off: 01/12/2019 (post hoc, required by G-BA in connection with the expiry)	Primary: metastasis-free survival Secondary: outcomes of the categories of mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes.
b. During continuous administration of ADT: 3 PSA rises measured at least 1 week apart, with the last PSA > 2ng/mL.
c. Outcome-specific information is provided in Table 8.

ADT: androgen deprivation therapy; AE: adverse event; N: number of randomized (included) patients; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; RCT: randomized controlled trial

Table 7: Characterization of the interventions – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study	Intervention	Comparison
SPARTAN	Apalutamide 240 mg/day + ADT[a]	Placebo + ADT[a]
	Prior treatment Disallowed ▪ CYP17 inhibitors (e.g. abiraterone acetate, ketoconazole) ▪ radiopharmaceutical substances (e.g. strontium-89) or immunotherapy (e.g. sipuleucel-T) for nmCRPC ▪ chemotherapy (except adjuvant/neoadjuvant) ▪ second-generation antiandrogens (e.g. enzalutamide) **Concomitant treatment** Not recommended ▪ strong CYP3A4 inducers and CYP3A4 substrates with narrow therapeutic indices ▪ strong CYP2C8 inhibitors (e.g. gemfibrozil) Disallowed ▪ approved drugs for prevention of skeletal-related events in patients with solid tumours (e.g. denosumab); allowed for treatment of osteoporosis in the appropriate doses, provided that therapy regimen had been stable for 4 weeks before randomization ▪ drugs known to lower the seizure threshold Allowed ▪ radiotherapy for locoregional pelvic disease; surgical interventions for treatment of local progression or of symptoms (e.g. transurethral resection of the prostate) ▪ systemic corticosteroids (short-term use ≤ 4 weeks allowed if clinically indicated)	

a. Surgical castration or continuous treatment with GnRH analogues for ≥ 4 weeks prior to randomization with testosterone levels < 50 ng/dL.

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

Study design

The SPARTAN study is a randomized, double-blind, multicentre study which compares apalutamide in combination with ADT with treatment with ADT and the additional administration of placebo. Included were adult men with nmCRPC who are at high risk of developing metastases. The presence of high-risk prostate cancer was defined by a prostate-specific antigen doubling time (PSADT) of ≤ 10 months. Patients with (distant) metastases were ineligible for study participation. However, the presence of pelvic lymph nodes < 2 cm along the short axis (N1) below the bifurcation of the iliac artery was allowed at study inclusion. Patients with symptomatic locoregional disorders requiring medical intervention (e.g. moderate or severe urinary tract obstruction or hydronephrosis due to the primary tumour) were excluded. Patients had to be in a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status of 0 or 1. Overall, the investigated patient population corresponds to patients with no or few symptoms. Included patients had to have either undergone surgical

castration or had to continue drug-based ADT using GnRH analogues in addition to the study drug. According to the inclusion criterion, the testosterone level had to be below 50 ng/dL.

In total, 1207 patients were randomized in a 2:1 ratio. Of these, 806 patients were included in the intervention arm of apalutamide + ADT and 401 patients in the control arm of placebo + ADT. Randomization was stratified by PSADT (≤ 6 months versus > 6 months), use of bone-preserving substances (yes/no), and the presence of locoregional disease (N0/N1).

Treatment with apalutamide was largely consistent with the SPC [19].

Treatment with the study drug was continued until documented radiographic progression (development of distant metastases), withdrawal of informed consent, or unacceptable toxicity. There were no restrictions regarding the type of subsequent therapy after treatment end. The choice of subsequent therapy was blinded. However, within the framework of the study, patients were explicitly offered the option of receiving abiraterone as subsequent systemic treatment, provided that the physician considered abiraterone the suitable treatment option for the individual patient and that abiraterone (together with prednisone or prednisolone) was an approved treatment option for metastatic castration-resistant prostate cancer in the respective country. For the data cut-off to be assessed, 1 December 2019, no information is available on the subsequent therapies administered.

The primary outcome of the study was MFS. Patient-relevant secondary outcomes were overall survival, symptomatic progression, health status, health-related quality of life, and AEs.

The study is still ongoing. So far, 3 data cut-offs are available:

- 1st data cut-off: 19 May 2017 (prespecified analysis; initial assessment A19-09)
- 2nd data cut-off: 1 February 2019 (post hoc)
- 3rd data cut-off: 1 December 2019 (post hoc, required by G-BA in connection with the expiry)

The present benefit assessment is based on the results of the data cut-off date of 1 December 2019.

The event-triggered prespecified final analysis is to be conducted after 427 deaths and expected to take place in the course of 2020.

Following the primary analysis, which was based on the 1st data cut-off on 19 May 2017, the study was unblinded on 22 July 2017 in accordance with the recommendation of the independent data monitoring committee. With Amendment 8 of the study protocol, patients who were still being treated in the control arm at the time of unblinding were given the option of switching to apalutamide treatment with simultaneous continuation of existing ADT. At the time of unblinding, 119 patients were still being treated in the control arm. Of these patients,

76 (19% of the patients originally randomized to the control arm) switched to apalutamide + ADT treatment. For the remaining 43 patients, the main reasons for not switching to apalutamide + ADT were disease progression before implementation of Amendment 8 of the study protocol in the individual study centre (n = 23) and lack of patient consent (n = 12).

Operationalization and implementation of the ACT

The G-BA defined watchful waiting while maintaining ongoing conventional ADT as the ACT. For the present benefit assessment, watchful waiting was operationalized as a follow-up strategy which particularly comprises diagnosis of disease progression (also see Section 2.3 of the initial assessment of apalutamide). In the SPARTAN study, regular visits took place at 16-week intervals for the patients of both treatment arms. During these visits, the patients underwent, among other measures, radiographic examination for metastases using computed tomography and bone scans. Overall, the diagnostic approach of the SPARTAN study is regarded as appropriate, and in connection with the continued administration of ADT in the study, the ACT (watchful waiting while maintaining ongoing conventional ADT) is considered adequately implemented.

Follow-up

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

Table 8: Planned follow-up observation – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SPARTAN	
Mortality	
Overall survival	Until death, lost to follow-up, or withdrawal of informed consent
Morbidity	
Symptomatic progression	Until death, lost to follow-up, or withdrawal of informed consent
Health status (EQ-5D VAS)	Up to 12 months after progression
Health-related quality of life (FACT-P)	Up to 12 months after progression
AEs	
All outcomes of the category	Up to 28 days after treatment discontinuation

a. After unblinding of the study, the outcome was assessed exclusively by the physician; see Section 2.4.3 for the operationalization.

ADT: androgen deprivation therapy; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; RCT: randomized controlled trial; VAS: visual analogue scale

In the SPARTAN study, the outcomes of overall survival and symptomatic progression were followed up until either death, lost to follow-up, or withdrawal of informed consent. Hence, information is available on these patient-relevant outcomes for the further patient follow-up strategy, which is also part of the comparator therapy of watchful waiting (as a consequence of the follow-up observation).

In contrast, the observation periods for further outcomes of the outcome categories of morbidity, health-related quality of life, and AEs were systematically shortened. For instance, the outcomes from the AE category were recorded only for the period of treatment with the study drug (plus 28 days). The outcomes of health status and health-related quality of life were observed beyond progression, but for no more than 12 months after progression. Moreover, despite the longer follow-up observation according to the statistical analysis plan, the analyses of the questionnaires European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) and the FACT-P only considered recordings until the time point at which follow-up treatment was initiated. However, to be able to draw a reliable conclusion on the total study period or the time until patient death, it would be necessary to record also these outcomes – e.g. overall survival – over the total period and include them in the analyses.

Characterization of the study population

Table 9 shows the patient characteristics in the included study.

Table 9: Characterization of the study population – RCT, direct comparison: apalutamide + ADT versus placebo + ADT (multi-page table)

Study Characteristics Category	**Apalutamide + ADT N[a] = 806**	**Placebo + ADT N[a] = 401**
SPARTAN		
Age [years], mean (SD)	74 (8)	74 (8)
Gleason score at initial diagnosis, n (%)		
< 7	152 (18.9[b])	72 (18.0[b])
7	291 (36.1[b])	146 (36.4[b])
> 7	341 (42.3[b])	169 (42.1[b])
Unknown	22 (2.7)[b]	14 (3.5)[b]
Disease duration: time between initial diagnosis and randomization [years], median [min; max]	8.0 [0.3; 30.4]	7.9 [0.8; 26.3]
PSA doubling time[c], n (%)		
≤ 6 months	576 (71.5)	284 (70.8)
> 6 months	230 (28.5)	117 (29.2)
ECOG-PS, n (%)		
0	623 (77.3)	311 (77.6[b])
1	183 (22.7)	89 (22.2[b])
Unknown	0 (0)	1 (0.2)[b]
Lymph node involvement at the start of the study (N classification)[c], n (%)		
N0	673 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Use of bone-protective drugs[c], n (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
Prior orchiectomy, n (%)	47 (5.8)	24 (6.0)
Prior hormonal therapy, n (%)		
GnRH analogues	780 (96.8)	387 (96.5)
First-generation antiandrogens	592 (73.4)	290 (72.3)
Other	17 (2.1)	9 (2.2)
Region, n (%)		
North America	285 (35.4)	134 (33.4)
Europe	395 (49.0)	204 (50.9)
Rest of the world	126 (15.6)	63 (15.7)
Treatment discontinuation, n (%)	ND[d]	ND[d]
Study discontinuation, n (%)	ND[d]	ND[d]

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. IQWiG calculations.
c. Stratification characteristic according to IVRS.
d. Data unavailable for the current data cut-off.

Table 9: Characterization of the study population – RCT, direct comparison: apalutamide + ADT versus placebo + ADT (multi-page table)

Study **Characteristics** **Category**	**Apalutamide + ADT** **N[a] = 806**	**Placebo + ADT** **N[a] = 401**
ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; GnRH: gonadotropin-releasing hormone; IVRS: Interactive Voice Response System; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; PSA: prostate specific antigen; RCT: randomized controlled trial; SD: standard deviation		

The demographic and clinical characteristics are balanced in the 2 study arms. The mean age of the patients was 74 years, and approximately 50% of the patients were from Europe. The median time of diagnosis of prostate cancer was almost 8 years prior to randomization. About 16% of the patients had lymph node involvement at the start of the study. In most patients (about 97%), ADT was performed by medical castration using GnRH analogues. Almost 6% of the patients had prior orchiectomy.

Duration of treatment and follow-up observation

Table 10 shows the median treatment duration and observation period of the patients for individual outcomes, to the extent available.

Table 10: Information on the course of the study – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study **Duration of the study phase** **Outcome category**	**Apalutamide + ADT** **N = 806**	**Placebo + ADT** **N = 401**
SPARTAN		
Treatment duration [months]		
Median [min; max]	32.85 [ND; ND]	11.48 [ND; ND]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[a]	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
AEs	ND	ND
a. The median observation period was 50.56 months for the patients of both treatment arms. No information is available for the individual study arms.		
ADT: androgen deprivation therapy; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation		

The median treatment duration in the intervention arm of the study was substantially longer than in the control arm (32.9 versus 11.5 months).

The median observation period for the outcome of overall survival was 50.6 months for the patients of both treatment arms. For all other outcomes, no data on the observation period were available.

For AE outcomes, the differences in treatment and observation duration are assumed to be similar because AE data were recorded for only up to 28 days after treatment discontinuation.

Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Providers			
SPARTAN	Yes	Yes	No[a]	No[a]	Yes	Yes	Low

a. After the primary analysis, the study was unblinded.

ADT: androgen deprivation therapy; RCT: randomized controlled trial

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

Following the primary analysis, which was based on the 1st data cut-off, the SPARTAN study was unblinded (see Section 2.3.2). Restrictions resulting from the open-label study design after unblinding of the study are described in Section 2.4 under risk of bias at outcome level.

Transferability to the German healthcare context

The company reports that the purpose of the SPARTAN study is to evaluate apalutamide in high-risk nmCRPC patients, regardless of the reasons for prior therapy in the non-metastatic, hormone-sensitive disease stage. The decision on the start and type of castration in this disease stage was reportedly at the medical discretion of the treating physicians in the country-specific healthcare context.

The company explains that for patients with localized prostate cancer who reject curative therapy or watchful waiting, the German S3 guideline recommends, at the second highest evidence level, immediate ADT [20]. It states that in the SPARTAN study, some 25% of patients received no local therapy with curative intent and that for them, immediate ADT would have been indicated as per the guideline.

Contrary to international guidelines, the German S3 guideline's treatment recommendations reportedly rested on the assumption of a more restrictive use of ADT in patients with prostate-specific antigen (PSA) recurrence or PSA progression of recurrent prostate cancer. According to the company, much more complex decision-making processes are actually involved in establishing the indication for ADT in the German healthcare system in a non-metastatic, hormone-sensitive disease stage after biochemical recurrence and exhaustion of all options of curative intent.

The company cites a market research study on the actual treatment situation of hormone-sensitive prostate cancer patients without distant metastases in Germany [21]. Accordingly, after the initial diagnosis and decision against therapy with curative intent, ADT monotherapy is the preferred option, followed by maximum androgen blockade. The company states further that alongside the criteria defined in the German S3 guideline, factors considered particularly relevant for the decision are the remaining life expectancy, patient preferences as well as the Gleason score. The company concludes that the German healthcare reality is based not as much on the German S3 guideline, but more so on the recommendations of European guidelines, asserting that there were no reasons to question the representativeness of the SPARTAN study population for the German healthcare context.

The company does not present any further information on the transferability of study results to the German healthcare context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptomatic progression
  - health status (measured using the EQ-5D VAS)
- Health-related quality of life
  - measured using the FACT-P total score
- AEs
  - serious AEs (SAEs)
  - severe AEs of CTCAE grade ≥ 3
  - discontinuation due to AEs
  - further specific AEs, if any

The selection of patient-relevant outcomes departs from the selection by the company, which uses further outcomes in Module 4 A of the dossier (for the reasoning, also see Section 2.7.4.3.2 of the initial assessment of apalutamide). For a discussion on the outcome of MFS as a surrogate outcome of overall survival, see Appendix D of the full dossier assessment. Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study	Outcomes							
	Overall survival	Symptomatic progression[a]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Other specific AEs[b]
SPARTAN	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes

a. Defined as one of the following events:
- skeletal-related events (pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone),
- pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy,
- clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy.

b. The following events are considered (MedDRA coding): "arthralgia (PT, AE)", "skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)", "nervous system disorders (SOC, AEs)", "renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)", "hypothyroidism (PT, AEs)", "infections and infestations (SOC, SAE)" and "injury, poisoning, and procedural complications (SOC, SAEs)".

c. No usable data available.

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

For the following outcome, no usable data are available:

- Health status (as measured using EQ-5D VAS): Regarding the outcome of health status as measured using EQ-5D VAS, Module 4 A of the company's dossier presents time to event analyses on improvement by ≥ 7 points and deterioration by ≥ 10 points. The recording of health status using the VAS is deemed patient relevant. Concerning the

validity of these minimum important differences (MID), the company refers to Pickard 2007 [22]. However, the cited publication is unsuitable for demonstrating the validity of MID for EQ-5D VAS [23]. The MIDs used by the company are therefore disregarded. Nevertheless, the analyses submitted by the company are presented as supplementary information in Appendix C of the full dossier assessment. The company's dossier does not provide any data on mean differences in the EQ-5D VAS.

2.4.2 Risk of bias

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

Table 13: Risk of bias at study and outcome levels – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study	Study level	Outcomes							
		Overall survival	Symptomatic progression[a]	Health status EQ-5D VAS	Health-related quality of life (FACT-P)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Other specific AEs[b]
SPARTAN	L	H[c]	H[c, d]	–[e]	H[c, f, g]	H[g]	H[f]	H[g]	H[f, g]

a. Defined as occurrence of one of the following events:
- skeletal-related events (pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone),
- pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy,
- clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy.

b. The following events are considered (MedDRA coding): "arthralgia (PT, AE)", "skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)", "nervous system disorders (SOC, AEs)", "renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)", "hypothyroidism (PT, AEs)", "infections and infestations (SOC, SAE)" and "injury, poisoning, and procedural complications (SOC, SAEs)".

c. Relevant extent of planned treatment switching.

d. After unblinding of the study, the outcome was assessed exclusively by the physician.

e. No usable data available.

f. The outcome collector was not blinded; among further specific AEs, this applies only to "arthralgia (PT, AE)", "nervous system disorders (SOC, AEs)", and "hypothyroidism (PT, AEs)".

g. Incomplete observations for potentially informative reasons at different periods of consideration of recordings or different observation periods.

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

The risk of bias of the results for the outcome of overall survival is rated as high. This is due to the relevant extent of planned treatment switching (19% of patients originally randomized to the control arm).

This departs from the assessment by the company, which deems the outcome of overall survival to have a low risk of bias.

All other outcomes, except for the outcomes of systematic progression and discontinuation due to AEs, are rated as having a high risk of bias due to the different lengths of observation periods for potentially informative reasons and the resulting incomplete observations.

The outcome of symptomatic progression is deemed to have a high risk of bias since the outcome was assessed exclusively by the respective physician after the study had been unblinded. In this process, the physicians had access to the PSA values, and the radiographic scans were no longer assessed by a blinded independent central review.

For the outcomes of symptomatic progression and FACT-P, the extent of planned treatment switches further contributed to the high risk of bias.

For the FACT-P and the outcomes of discontinuation due to AEs as well as individual specific AEs (arthralgia [PT], nervous system disorders [SOC], and hypothyroidism [PT]), the open-label study design after unblinding the study further contributes to a high risk of bias.

The company concurs in that the outcomes of symptomatic progression, FACT-P, and AE outcomes are associated with a high risk of bias.

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of apalutamide + ADT with placebo + ADT in patients with nmCRPC who have a high risk of developing metastases. Kaplan-Meier curves on the presented time-to-event analyses are found in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment. Where necessary, the data from the company's dossier are complemented by IQWiG calculations. The company did not report the p-values of the results in Module 4 A of the dossier.

Table 14: (Mortality, morbidity, health-related quality of life, and AEs, time to event) – RCT, indirect comparison: apalutamide + ADT versus placebo + ADT (multi-page table)

Study Outcome category Outcome	Apalutamide + ADT		Placebo + ADT		Apalutamide + ADT vs. placebo + ADT
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a] p-value
SPARTAN					
Mortality					
Overall survival	806	66.10 [61.34; NC] 261 (32.4)	401	58.68 [52.70; NC] 149 (37.2)	0.77 [0.63; 0.94]; ND
Morbidity					
Symptomatic progression	806	NA 149 (18.5)	401	NA 102 (25.4)	0.58 [0.45; 0.75]; ND
Skeletal-related events (pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone)	806	NA 51 (6.3)	401	NA 33 (8.2)	0.64 [0.41; 0.99]; ND
Pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy	806	NA 77 (9.6)	401	NA 54 (13.5)	0.60 [0.42; 0.85]; ND
Clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy	806	NA 45 (5.6)	401	NA 31 (7.7)	0.62 [0.39; 0.97]; ND
Health-related quality of life					
FACT-P					
Total score, time to deterioration[b]	806	6.60 [5.55; 8.28] 544 (67.5)	401	8.38 [6.47; 12.95] 230 (57.4)	1.04 [0.89; 1.22]; ND
Prostate cancer-specific subscale[c]	806	3.84 [3.71; 4.70] 619 (76.8)	401	3.78 [2.86; 4.80] 272 (67.8)	0.97 [0.84; 1.13]; ND
Physical well-being[c]	806	6.57 [5.55; 8.38] 530 (65.8)	401	7.43 [5.59; 11.11] 234 (58.4)	0.97 [0.83; 1.14]; ND
Social/family well-being[c]	806	7.49 [5.62; 11.11] 473 (58.7)	401	4.90 [3.84; 8.38] 223 (55.6)	0.87 [0.73; 1.02]; ND
Emotional well-being[c]	806	14.69 [11.07; 18.63] 459 (56.9)	401	14.82 [10.61; 32.99] 181 (45.1)	1.06 [0.89; 1.27]; ND
Functional well-being[c]	806	4.63 [3.78; 5.59] 558 (69.2)	401	6.51 [4.70; 9.27] 229 (57.1)	1.15 [0.98; 1.35]; ND

Table 14: (Mortality, morbidity, health-related quality of life, and AEs, time to event) – RCT, indirect comparison: apalutamide + ADT versus placebo + ADT (multi-page table)

Study Outcome category Outcome	Apalutamide + ADT		Placebo + ADT		Apalutamide + ADT vs. placebo + ADT
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a] p-value
AEs					
AEs (supplementary information)	803	0.56 [0.43; 0.70] 781 (97.3)	398	0.76 [0.53; 0.92] 373 (93.7)	1.14 [1.00; 1.29]; ND
SAEs	803	35.06 [31.34; 41.92] 295 (36.7)	398	35.25 [28.19; NC] 100 (25.1)	0.84 [0.67; 1.07]; ND
Severe AEs (CTCAE grade ≥ 3)	803	21.91 [18.46; 25.92] 450 (56.0)	398	24.15 [18.53; 29.47] 146 (36.7)	1.10 [0.91; 1.34]; ND
Discontinuation due to AEs	803	NA [54.41; NC] 115 (14.3)	398	NA 29 (7.3)	1.40 [0.92; 2.12]; ND
Arthralgia (PT, AEs)	803	57.20 [45.17; NC] 158 (19.7)	398	NA 33 (8.3)	1.74 [1.19; 2.54]; ND
Skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)	803	NA 52 (6.5)	398	NA 1 (0.3)	23.84 [3.29; 172.53]; ND
Nervous system disorders (SOC, AEs)	803	37.16 [30.42; 47.80] 326 (40.6)	398	NA 93 (23.4)	1.54 [1.22; 1.94]; ND
Renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)	803	NA [58.91; NC] 67 (8.3)	398	NA [35.48; NC] 46 (11.6)	0.38 [0.25; 0.57]; ND
Hypothyroidism (PT, AEs)	803	NA 59 (7.3)	398	NA 5 (1.3)	4.43 [1.77; 11.09]; ND
Infections and infestations (SOC, SAEs)	803	NA [53.09; NC] 76 (9.5)	398	NA 9 (2.3)	2.29 [1.13; 4.64]; ND
Injury, poisoning, and procedural complications (SOC, SAEs)	803	NA [59.37; NC] 60 (7.5)	398	NA 6 (1.5)	2.82 [1.20; 6.61]; ND

a. HR and CI: Cox proportional hazards model with treatment as the only explanatory variable, stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).
b. Time to deterioration by ≥ 10 points.
c. Time to deterioration by ≥ 3 points.

Table 14: (Mortality, morbidity, health-related quality of life, and AEs, time to event) – RCT, indirect comparison: apalutamide + ADT versus placebo + ADT (multi-page table)

Study Outcome category Outcome	Apalutamide + ADT		Placebo + ADT		Apalutamide + ADT vs. placebo + ADT
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a] p-value
ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; MID: minimal important difference; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class					

Table 15: Results (morbidity, continuous) – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study Outcome category Outcome	Apalutamide + ADT			Placebo + ADT			Apalutamide + ADT versus placebo + ADT
	N	Values at baseline mean (SD)	Change Mean (SD)	N	Values at baseline mean (SD)	Change mean (SD)	Effect [95% CI]; p-value
SPARTAN							
Morbidity							
Health status (EQ-5D VAS)	No usable data[a]						
a. In Module 4 A of its dossier, the company does not present any analyses of mean differences. ADT: androgen deprivation therapy; CI: confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; N: number of analysed patients; RCT: randomized controlled trial; SD: standard error; VAS: visual analogue scale							

Due to the high risk of bias, the available data allow deriving at most hints, e.g. of an added benefit, for all examined outcomes. For some specific outcomes, high certainty of results is nevertheless assumed in consideration of the 1st data cut-off (see description of the results below).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found between treatment arms in favour of apalutamide + ADT in comparison with placebo + ADT. This

results in a hint of an added benefit in favour of apalutamide + ADT in comparison with watchful waiting + ADT.

This assessment of added benefit deviates from that of the company, which derived an indication of added benefit.

Morbidity

Symptomatic progression

The outcome of symptomatic progression is a combined outcome which includes the following events:

- development of a skeletal-related event (pathological fractures, compression of the spinal cord, or requirement of a surgical intervention or radiation therapy of the bone),
- pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy as well as
- development of clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy.

For the outcome of symptomatic progression, a statistically significant difference between treatment arms was found in favour of apalutamide + ADT in comparison with placebo + ADT. Considered together with the results from the 1st data cut-off from 19 May 2017 (also see Section 2.4.3 of the initial assessment of apalutamide), this outcome is deemed to have a high certainty of results despite the high risk of bias. This results in an indication of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT.

However, the chosen operationalization of this outcome is unsuitable for comprehensively recording the events of pain progression or progression of other disease-related symptoms. Connecting symptoms with initiation of systemic therapy, as was done in the study, is insufficient for an adequately sensitive recording of the events of symptomatic progression. It is assumed that, in some cases in the SPARTAN study, symptomatic progression of disease occurred without resulting in a change of systemic anticancer treatment. Patients with symptomatic progression of disease who decided against a new systemic therapy but opted for supportive, symptom-alleviating treatment (e.g. escalation or initiation of pain management with opioids) were not recorded here. It is unclear whether and how effect estimation would change if the events of progression which are not connected with systemic treatment had also been recorded (see also Section 2.7.4.3.2 of the initial assessment of apalutamide). For this reason, the extent of added benefit cannot be quantified for the outcome of symptomatic progression.

The company also derived an indication of an added benefit.

Health status (EQ-5D VAS)

No usable data are available for the outcome of health status as measured using EQ-5D VAS. Consequently, there is no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

FACT-P

For health-related quality of life as measured using the FACT-P, no statistically significant difference between treatment arms was found. Consequently, there is no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

This concurs with the company's assessment.

AEs

SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs

For each of the outcomes of SAEs, severe AEs (CTCAE ≥ grade 3), and discontinuation due to AEs, no statistically significant difference between treatment arms was found. For each of these outcomes, this results in no hint of greater or lesser harm of apalutamide + ADT in comparison with watchful waiting + ADT; therefore, there is no proof of greater or lesser harm.

This concurs with the company's assessment.

Specific AEs

Arthralgia (preferred term [PT], AEs), nervous system disorders (SOC, AEs), hypothyroidism (PT, AEs), infections and infestations (SOC, SAEs), injury, poisoning, and procedural complications (SOC, SAEs)

For each of the outcomes of arthralgia (PT, AEs), nervous system disorders (SOC, AEs), hypothyroidism (PT, AEs), infections and infestations (SOC, SAEs), and injury, poisoning, and procedural complications (SOC, SAEs), a statistically significant difference was found to the disadvantage of apalutamide + ADT in comparison with placebo + ADT. For each of these outcomes, this results in a hint of greater harm of apalutamide + ADT in comparison with watchful waiting + ADT.

This departs from the assessment by the company, which presents the results on these outcomes, but does not derive any lesser or greater harm from them.

Skin and subcutaneous tissue disorders, severe AEs (SOC, severe AEs [CTCAE grade ≥ 3]):

For the outcome of skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was found to the disadvantage of apalutamide + ADT

in comparison with placebo + ADT. Despite the high risk of bias, a high certainty of results is assumed due to the effect size. This results in an indication of greater harm of apalutamide + ADT in comparison with watchful waiting + ADT.

The assessment of added benefit departs from the assessment by the company, which presents the results on this outcome, but does not derive any lesser or greater harm from them.

Severe AEs (CTCAE grade ≥ 3): Renal and urinary disorders (SOC)

For the outcome of renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), a statistically significant difference was found in favour of apalutamide + ADT in comparison with placebo + ADT. This results in a hint of lesser harm of apalutamide + ADT in comparison with watchful waiting + ADT. Overall, however, it is questionable whether the effect is actually to be attributed to the outcome category of AEs or whether it rather reflects the disease symptoms. The events occurring under the SOC comprised typical locoregional symptoms of prostate cancer, e.g. urinary retention and hydronephrosis.

This departs from the assessment by the company, which presents the results on this outcome, but does not derive any lesser or greater harm from them.

2.4.4 Subgroups and other effect modifiers

The present assessment accounts for the following potential effect modifier:

- age (< 65 years/≥ 65 to < 75 years/≥ 75 years)

This attribute was predefined for the outcomes of overall survival and MFS.

Interaction tests are conducted whenever at least 10 patients per subgroup are included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

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

Subgroup analyses are available for all outcomes except for health status (EQ-5D VAS, analysed using change from baseline).

Table 16 shows the results of the subgroup analyses.

Table 16: Subgroups (mortality, time to event) – RCT, direct comparison: apalutamide + ADT versus placebo + ADT

Study Outcome Characteristic Subgroup	Apalutamide + ADT N	Apalutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Apalutamide + ADT vs. placebo + ADT HR [95% CI][a]	Apalutamide + ADT vs. placebo + ADT p-value
SPARTAN						
Overall survival						
Age						
< 65 years	106	NA 16 (15.1)	43	NA [39.26; NC] 14 (32.6)	0.31 [0.15; 0.65]	ND
≥ 65 to < 75 years	307	66.10 [65.05; NC] 98 (31.9)	169	67.38 [58.61; NC] 51 (30.2)	1.00 [0.71; 1.41]	ND
≥ 75 years	393	57.82 [53.06; 61.96] 147 (37.4)	189	49.94 [45.21; 59.89] 84 (44.4)	0.76 [0.58; 0.996]	ND
Total					Interaction:	0.0202[b]

a. HR and CI: Cox proportional hazards model with treatment as the only explanatory variable, stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).
b. Cox proportional hazards model with corresponding interaction term.
c. IQWiG calculations via meta-analysis.

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; n:number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; RCT: randomized controlled trial

For the outcome of overall survival, the available subgroup results show an effect modification by the attribute of age. For patients < 65 years of age and for those ≥ 75 years of age, a statistically significant effect was found in favour of apalutamide + ADT in comparison with placebo + ADT. In contrast, for patients of the subgroup ≥ 65 to < 75 years of age, there is no statistically significant difference between treatment arms, with the effect estimator being close to the zero effect. Since the subgroup analysis for the middle age group shows considerably different results from those of the subgroups < 65 years and ≥ 75 years, the result of this subgroup analysis is deemed not meaningful.

This assessment concurs with the company's approach.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated on the basis of the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for morbidity and AE outcomes

Not in all cases does the dossier indicate whether the outcomes considered in the present benefit assessment were serious/severe or non-serious/non-severe. For these outcomes, an explanation for the allocation is provided below.

The outcome of symptomatic progression has been assigned to the category of serious/severe symptoms/late complications.

Each of the specific AEs of arthralgia, nervous system disorders, and hypothyroidism are outcomes of the category of non-serious/non-severe AEs because most of the events included in these outcomes are non-serious/non-severe.

Table 17: Extent of added benefit at outcome level: apalutamide + ADT versus placebo + ADT (multi-page table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Apalutamide + ADT vs. placebo + ADT** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	66.10 vs. 58.68 HR: 0.77 [0.63; 0.94]; ND Probability: hint	Outcome category: Mortality $0.85 \leq CI_u < 0.95$ Added benefit, extent: considerable
Morbidity		
Symptomatic progression	NA vs. NA HR: 0.58 [0.45; 0.75]; ND Probability: indication	Outcome category: serious/severe symptoms / late complications Added benefit, extent: non-quantifiable[c]
Skeletal-related events (pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone)	NA vs. NA HR: 0.64 [0.41; 0.99]; ND	
Pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy	NA vs. NA HR: 0.60 [0.42; 0.85]; ND	
Clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy	NA vs. NA HR: 0.62 [0.39; 0.97]; ND	
Health status (EQ-5D VAS)	No usable data	Lesser/added benefit not proven
Health-related quality of life		
FACT-P total score		
Deterioration	6.60 vs. 8.38 HR: 1.04 [0.89; 1.22]; ND	Lesser/added benefit not proven
AEs		
SAEs	35.06 vs. 35.25 HR: 0.84 [0.67; 1.07]; ND	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	21.91 vs. 24.15 HR: 1.10 [0.91; 1.34]; ND	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: apalutamide + ADT versus placebo + ADT (multi-page table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Apalutamide + ADT vs. placebo + ADT** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	NA vs. NA HR: 1.40 [0.92; 2.12]; ND	Greater/lesser harm not proven
Arthralgia (PT, AEs)	57.20 vs. NA HR: 1.74 [1.19; 2.54]; HR[d]: 0.57 [0.39; 0.84]; ND Probability: hint	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_o < 0.90$ Greater harm; extent: minor
Skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 23.84 [3.29; 172.53]; HR[d]: 0.04 [0.01; 0.30]; ND Probability: indication	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: considerable
Nervous system disorders (SOC, AEs)	37.16 vs. NA HR: 1.54 [1.22; 1.94] HR[d]: 0.65 [0.52; 0.82] ND Probability: hint	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_u < 0.90$ Greater harm; extent: minor
Renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 0.38 [0.25; 0.57]; ND Probability: hint	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% Lesser harm; extent: considerable
Hypothyroidism (PT, AEs)	NA vs. NA HR: 4.43 [1.77; 11.09]; HR[d]: 0.23 [0.09; 0.56]; ND Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Infections and infestations (SOC, SAEs)	NA vs. NA HR: 2.29 [1.13; 4.64]; HR[d]: 0.44 [0.22; 0.88]; ND Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_o < 0.90$ greater harm; extent: considerable
Injury, poisoning, and procedural complications (SOC, SAEs)	NA vs. NA HR: 2.82 [1.20; 6.61]; HR[d]: 0.35 [0.15; 0.83]; ND Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ greater harm; extent: considerable

Table 17: Extent of added benefit at outcome level: apalutamide + ADT versus placebo + ADT (multi-page table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Apalutamide + ADT vs. placebo + ADT** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability given if a statistically significant and relevant effect is present. b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u). c. The operationalization of this outcome is unsuitable for comprehensively recording the events of pain progression or progression of other disease-related symptoms. It is unclear how potentially unrecorded events effect the extent of added benefit. d. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit. ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; NA: not achieved; ND: no data; PT: preferred term; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale		

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of apalutamide + ADT compared with watchful waiting + ADT

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival: Hint of added benefit – extent: considerable	–
Serious/severe symptoms / late complications Symptomatic progression: Indication of added benefit – extent: non-quantifiable	–
Serious/severe AEs[a] Renal and urinary disorders (severe AEs): Hint of lesser harm – extent: considerable	Serious/severe AEs Diseases of the skin and subcutaneous tissue (severe AEs): Indication of greater harm – extent: considerable Infections and infestations (SAEs), injury, poisoning, and procedural complications (SAEs): for each, hint of greater harm – extent: considerable
–	Non-serious/non-severe AEs Arthralgia, nervous system disorders: for each, hint of greater harm – extent: minor Hypothyroidism: Hint of greater harm – extent: considerable
a. It is questionable whether the outcome is actually to be allocated to the outcome category of adverse events or whether it rather reflects the symptoms of the disease. ADT: androgen deprivation therapy; AEs: adverse events; SAEs: serious adverse events	

In terms of favourable effects, the aggregate view of results reveals an indication of non-quantifiable added benefit in the morbidity outcome category as well as a hint of considerable added benefit for the outcome of overall survival. Moreover, there is 1 hint of another favourable effect in the category of serious/severe AEs. However, it is questionable whether the favourable effect on the outcome of renal and urinary disorders is actually to be allocated to the outcome category of AEs or whether it rather reflects the symptoms of the disease. An unequivocal differentiation is impossible on the basis of the available information.

The favourable effects are offset by 1 indication and several hints of unfavourable effects in the outcome category of AEs, some of major and some of considerable extent. Overall, however, the unfavourable effects do not completely offset the favourable effects.

All things considered, for patients with nmCRPC and a high risk of developing metastases, there is an indication of considerable added benefit of apalutamide + ADT in comparison with the ACT of watchful waiting + ADT.

Table 19 presents a summary of the result of the benefit assessment of apalutamide in comparison with the ACT.

Table 19: Apalutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with nonmetastatic castration-resistant prostate cancer who have a high risk of developing metastases	Watchful waiting while maintaining ongoing conventional ADT[b]	Indication of considerable added benefit
a. Presentation of the respective ACT specified by the G-BA. b. Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone		

The above assessment concurs with that of the company.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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