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Apalutamide (prostate cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Apalutamide (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-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	non-metastatic 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
SGB	Sozialgesetzbuch (Social Code Book)

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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 24 January 2019.

Research question

The aim of the present report was the assessment of the added benefit of apalutamide in comparison with the appropriate comparator therapy (ACT) "watchful waiting while maintaining ongoing conventional ADT" in adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who have a high risk of developing metastases.

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

Table 2: Research question of the benefit assessment of apalutamide

Subindication	**ACT**[a]
Adult men with nmCRPC who have a high risk of developing metastases	Watchful waiting while maintaining ongoing conventional ADT[b]
a: Presentation of the ACT specified by the G-BA. b: Surgical castration or medical castration through treatment with GnRH agonists or GnRH antagonists. ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone	

The company claimed to follow the G-BA's specification, but cited the conventional ADT (and not "watchful waiting while maintaining ongoing conventional ADT") as ACT.

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

Results

The SPARTAN study was included for the assessment of the added benefit of apalutamide in patients with nmCRPC who have a high risk of developing metastases.

Study design

The SPARTAN study was a randomized, double-blind study that compared apalutamide in combination with ADT with treatment with ADT and the additional administration of placebo. Included were adult men with high risk nmCRPC. The included patients either had to have

undergone surgical castration or they had to continue drug-based ADT using gonadotropin-releasing hormone (GnRH) analogues in addition to the study medication.

A total of 1207 patients were randomly assigned to both study arms in a 2:1 ratio. Treatment with apalutamide was implemented without relevant deviations from the specifications of the Summary of Product Characteristics (SPC).

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

The study is ongoing. After the planned and present data cut-off (19 May 2017), the study was unblinded and the patients were allowed to switch from the placebo arm to the apalutamide arm.

Risk of bias

The risk of bias across outcomes was rated as low for the study. The outcome-specific risk of bias was considered to be high for all outcomes except for "overall survival", "symptomatic progression" and "discontinuation due to AEs".

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

Morbidity

Symptomatic progression

The outcome "symptomatic progression" is a combined outcome that includes the following events:

- development of a skeletal-related event (pathological fractures, compression of the spinal cord or requirement of a surgical intervention or radiotherapy 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.

A statistically significant difference between the treatment arms in favour of apalutamide + ADT in comparison with placebo + ADT was shown for the outcome "symptomatic

progression". This resulted in an indication of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT.

Recording of the outcome "symptomatic progression" in the SPARTAN study is appreciated. However, the chosen operationalization of this outcome is unsuitable for extensive recording of the pain progression or the progression of other disease-related symptoms. Connection of the symptoms with the initiation of a systemic treatment, as it was done in the study, was insufficient for a sensitive recording of the events involved in symptomatic progression. It must be assumed that symptomatic progression of the disease occurred in the SPARTAN study without resulting in a change of the systemic anticancer treatment. Patients with symptomatic progression of the disease who decided against a new systemic therapy, but opted for supportive, symptom-alleviating treatment (e.g. escalation or initiation of a pain therapy with opioids) were not recorded here. It is unclear whether and how effect estimation would change when the events of the progression not connected with the systemic therapy had also been recorded. Therefore, the extent of added benefit cannot be quantified for the outcome "symptomatic progression".

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

Based on the mean differences, no statistically significant difference between the treatment arms was shown for the outcome "health status measured with the EQ-5D VAS". This resulted in 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

The outcome "health-related quality of life" was recorded using the Functional Assessment of Cancer Therapy – Prostate (FACT-P). No statistically significant difference between the treatment arms was shown for "time to deterioration" in the FACT-P total score. This resulted in no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT for the outcome "health-related quality of life".

Side effects

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

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs". Hence, for these outcomes there was no hint of greater or lesser harm from apalutamide + ADT in comparison with watchful waiting + ADT; greater or lesser harm is therefore not proven.

Specific AEs

- specific severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of apalutamide + ADT in comparison with placebo + ADT was found for the outcomes "skin and subcutaneous tissue disorders (System Organ Class [SOC])" and "general disorders and administration site conditions (SOC)".

Due to the high risk of bias, this resulted in a hint of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT for the outcome "general disorders and administration site conditions".

Despite the high risk of bias, a high certainty of conclusions was assumed for the outcome "skin and subcutaneous tissue disorders" due to the effect size, and an indication of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT was derived.

A statistically significant difference in favour of apalutamide + ADT in comparison with placebo + ADT was shown for the outcome "renal and urinary disorders (SOC)". This resulted in a hint of lesser harm from apalutamide + ADT in comparison with watchful waiting + ADT. However, it is overall questionable whether the effect must actually be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the diseases.

- Specific SAEs

A statistically significant difference to the disadvantage of apalutamide + ADT in comparison with placebo + ADT was shown for the outcome "injury, poisoning and procedural complications (SOC)". This resulted in a hint of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT.

- Specific AEs

A statistically significant difference to the disadvantage of apalutamide + ADT in comparison with placebo + ADT was shown for the outcomes "arthralgia" (preferred term [PT]), "nervous system disorders" (SOC) and "hypothyroidism" (PT). This resulted in a hint of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT.

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 apalutamide in comparison with the ACT are assessed as follows:

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

In the overall consideration, there was an indication of non-quantifiable added benefit in the outcome category "morbidity" and a hint of lesser harm regarding side effects with the extent "major" on the positive side. However, it is questionable whether the positive effect for the outcome "renal and urinary disorders" actually had to be allocated to the outcome category "side effects" or whether it rather reflected the symptoms of the diseases. Clear demarcation is not possible on the basis of the available information.

The positive effects were offset by one indication and several hints of negative effects in the outcome category "side effects", partly with major and considerable extents. However, these negative effects did not completely offset the positive effects, some of which achieved a major extent.

In the overall consideration of the results, there is an indication of considerable added benefit of apalutamide in comparison with the ACT "watchful waiting while maintaining ongoing conventional ADT" for patients with nmCRPC and a high risk of developing metastases. Table 3 presents a summary of probability and extent of the added benefit of apalutamide.

Table 3: Apalutamide – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with nmCRPC 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 ACT specified by the G-BA. b: Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone		

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

2.2 Research question

The aim of the present report was the assessment of the added benefit of apalutamide in comparison with the ACT "watchful waiting while maintaining ongoing conventional ADT" in adult men with nmCRPC who have a high risk of developing metastases.

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

Table 4: Research question of the benefit assessment of apalutamide

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

The company claimed to follow the G-BA's specification, but cited the conventional ADT (and not "watchful waiting while maintaining ongoing conventional ADT") as ACT. This deviation had no consequence for the present dossier assessment (see Section 2.7.1 of the full dossier assessment).

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on apalutamide (status: 16 January 2019)
- bibliographical literature search on apalutamide (last search on 16 January 2019)
- search in trial registries for studies on apalutamide (last search on 16 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on apalutamide (last search on 12 February 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
SPARTAN	Yes	Yes	No
a: Study sponsored by the company. ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SPARTAN	RCT, double-blind, parallel	Adult patients with high risk (PSADT ≤ 10 months), non-metastatic 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 until withdrawal of informed consent	234 centres in 26 countries in Europe, Asia, Australia, New Zealand, Russia, Canada and the United States 09.2013–ongoing Data cut-off: 19 May 2017	Primary: metastasis-free survival Secondary: outcomes of the categories "morbidity", "health-related quality of life", "AEs"

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: During continuous administration of ADT: increasing PSA values at 3 time points with intervals of at least 1 week and a last PSA value > 2 ng/ml.
c: Outcome-specific information is provided in Table 8.

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

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

Study	Intervention	Comparison
SPARTAN	Apalutamide 240 mg/day + ADT[a]	Placebo + ADT[a]
	Pretreatment not allowed: ▪ 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 anti-androgens (e.g. enzalutamide) **Concomitant treatment** not recommended: ▪ strong CYP3A4 inducers and CYP3A4 substrates with narrow therapeutic indices ▪ strong CYP2C8 inhibitors (e. g. gemfibrozil) not allowed: ▪ approved drugs for prevention of skeletal-related events in solid tumours (e.g. denosumab); allowed for treatment of osteoporosis in the appropriate doses provided that therapy regimen had been stable for 4 weeks prior to the start of the study ▪ drugs known to lower the threshold for seizures 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; GnRH: gonadotropin-releasing hormone; RCT: randomized controlled trial; vs.: versus

Study design

The SPARTAN study is a randomized, double-blind study which compares apalutamide in combination with ADT with a therapy with ADT and additional administration of placebo. Included were adult men with high risk nmCRPC. Presence of high risk prostate cancer was defined by a prostate-specific antigen doubling time (PSADT) of ≤ 10 months. Patients with (distant) metastases were not allowed to participate in the study. However, presence of pelvic lymph nodes < 2 cm along the short axis (N1) below the bifurcation of the arteria iliaca was allowed at study inclusion. Patients with symptomatic locoregional disorders requiring medical intervention (e.g. moderate or strong urinary tract obstruction or hydronephrosis due to the primary tumour) were excluded. Patients had to have a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Overall, the investigated patient population corresponded to patients with no or few symptoms. The

included patients either had to have undergone surgical castration or they had to continue drug-based ADT using GnRH analogues in addition to the study medication. In case of drug-based castration, the testosterone level should have been below 50 ng/dl.

Overall, a total of 1207 patients were randomly assigned to both study arms in a 2:1 ratio. Randomization was stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes/no) and the presence of locoregional diseases (N0/N1).

Treatment with apalutamide was largely implemented in accordance with the SPC [3]. In the course of the study, drug formulation was switched from 8 x 30 mg soft gel capsules per day to 4 x 60 mg tablets (suggested by the SPC) while maintaining randomization and blinding. Patients newly randomized at this time point received the new formulation of the drug. Patients who had received the drug in the soft gel capsule formulation were switched to the tablet form. It is assumed that a switch under maintenance of the total daily dose has no relevant impact on the results of the benefit assessment.

Treatment with the study medication took place until documented radiographic progression (development of distant metastases), withdrawal of informed consent or unacceptable toxicity.

21.7% of the patients in the apalutamide arm and 55.4% of the patients in the placebo arm received subsequent systemic therapy at the planned and present data cut-off (19 May 2017). There were no restrictions regarding the type of subsequent therapy after the end of the treatment. The choice of subsequent therapy was blinded. However, within the framework of the study, the patients were explicitly allowed to receive abiraterone as subsequent systemic treatment, provided that the physician considered abiraterone the suitable treatment option for the individual patient, and abiraterone (together with prednisone or prednisolone) was the approved treatment option for metastatic castration-resistant prostate cancer in the respective country. The most frequently administered subsequent therapies in the study were abiraterone (referring to patients who received subsequent therapy: 71.4% in the apalutamide arm or 72.5% in the placebo arm) and enzalutamide (referring to patients who received subsequent therapy: 11.4% or 12.6%).

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 “AEs”.

The study is ongoing. After the planned and present data cut-off (19 May 2017), the study was unblinded and the patients were allowed to switch from the placebo arm to the apalutamide arm.

Operationalization and implementation of the ACT

The G-BA specified “watchful waiting while maintaining ongoing conventional ADT” as ACT. For the present benefit assessment, watchful waiting was operationalized as a follow-up

strategy which particularly comprises diagnosis of disease progression. According to the current S3 guideline [4], imaging should not be routinely performed during follow-up care, and the patient should not be subjected to unnecessary examinations. Application of imaging techniques should be indicated precisely together with a specific research question and only when therapeutic consequences must be expected. For instance, indications for imaging include changes of the clinical state (symptom increase, change of general condition) that might require further therapies.

In the SPARTAN study, regular visits took place at 16-week intervals for the patients of both treatment arms. Among other things, the patients underwent radiographic examination with regard to metastases using computed tomography and bone scan during these visits. The S3 guideline does not foresee such regular radiographic examinations; however, given the 16-week rhythm, the examinations took place at rather long intervals. In case of suspected disease progression, radiographic examinations could be performed at an earlier point in time. Moreover, there were regular examinations on the development of skeletal-related events, pain progression or deterioration of health-related symptoms and on the development of clinically significant symptoms due to locoregional tumour progression (summarized under the outcome "symptomatic progression" in the study, see also Section 2.7.4.3.2 of the full dossier assessment), also beyond the end of treatment.

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

Treatment duration and follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SPARTAN	
Mortality	
overall survival	every 4 months until death, lost to follow-up or withdrawal of informed consent
Morbidity	
symptomatic progression[a]	every 4 months until death, lost to follow-up or withdrawal of informed consent
health status (EQ-5D VAS)	until 12 months after progression, every 4 months
Health-related quality of life (FACT-P)	until 12 months after progression, every 4 months
Side effects	
all outcomes in the category	up to 28 days after treatment discontinuation

a: For operationalization, see Section 2.7.4.3.2 of the full dossier assessment.

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

In the SPARTAN study, the outcomes “overall survival” and “symptomatic progression” were observed every 4 months until death, lost to follow-up or withdrawal of consent. Thus, data on these patient-relevant outcomes are available for the further follow-up strategy, which is also a component of the comparator therapy “watchful waiting” (as consequence of the observation).

The observation periods for the outcomes of further outcome categories, in contrast, were systematically shortened. Thus, outcomes from the category “side effects’ were recorded only for the period of treatment with the study medication plus 28 days. The outcomes “health status” and “health-related quality of life” were observed beyond progression, but at most until 12 month following progression. According to the statistical analysis plan (SAP), the analyses on the questionnaires EQ-5D and FACT-P only considered recordings until the time point at which follow-up treatment was initiated, irrespective of prolonged subsequent recording. However, to be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary to record all outcomes over the total period of time and to include them into the analyses.

Characteristics of the study population

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

Table 9: Characteristics of the study population – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT

Study Characteristics Category	**Apalutamide + ADT**	**Placebo + ADT**
SPARTAN	N[a] = 806	N[a] = 401
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, n (%)		
≤ 6 months	576 (71.5)	284 (70.8)
> 6 months	117 (29.2)	230 (28.5)
ECOG PS		
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), n (%)[c]		
N0	673 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Prior orchiectomy, n (%)	47 (5.8)	24 (6.0)
Prior hormonal therapy, n (%)		
GnRH analogues	780 (96.8)	387 (96.5)
First-generation anti-androgens	592 (73.4)	290 (72.3)
Other	17 (2.1)	9 (2.2)
Use of bone-protective drugs[c], n (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
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 (%)	314 (39.1)	279 (70.1)
Study discontinuation, n (%)	ND	ND

(continued)

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

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: Stratification characteristic according to IVRS
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; ND: no data; PSA: prostate-specific antigen; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

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

Follow-up

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

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

Study **Duration of the study phase** **Outcome category**	**Apalutamide + ADT**	**Placebo + ADT**
SPARTAN	N = 806	N = 401
Treatment duration [months]		
Median [min; max]	16.92 [0.1; 42.0]	11.17 [0.1; 37.1]
Mean (SD)	17.34 (9.5)	12.4 (8.0)
Observation period [months]		
Overall survival[a]	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a: The median observation period was 20.3 months for the patients of both treatment arms. There was no information for the individual study arms.
ADT: androgen deprivation therapy; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Median treatment duration in the intervention arm of the SPARTAN study is clearly longer than in the comparator arm (16.9 vs. 11.2 months). Thereby, the difference in the treatment

duration between the study arms must be ascribed to differing treatment discontinuation rates chiefly due to disease progression (19.3% in the apalutamide arm vs. 52.8% in the placebo arm).

With regard to the patients in both treatment arms, median duration of the follow-up observation of the outcome "overall survival" was 20.3 months. Data on the observation period for other outcomes were not available. For the outcomes on side effects, the differences in treatment and observation duration must be assumed to be similar, because they were only recorded 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 vs. placebo + ADT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
SPARTAN	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus							

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

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier 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

- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3.2 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of the outcomes – RCT, direct comparison: apalutamide + ADT vs. 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)	Further specific AEs[b]
SPARTAN	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Defined as occurrence of one of the following events:
- skeletal-related events (pathological fractures, compression of the spinal cord or requirement of a 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 were considered (MedDRA coding): "arthralgia (PT, AEs)", "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)" and "general disorders and administration site conditions (SOC, severe AEs CTCAE grade ≥ 3)", "injury, poisoning and procedural complications (SOC, SAEs)".

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life5 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; vs.: versus

2.4.2 Risk of bias

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

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT

Study		Outcomes							
	Study level	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)	Further specific AEs[b]
SPARTAN	Low	Low	Low	High[c]	High[c]	High[c]	Low	High[c]	High[c]

a: Defined as occurrence of one of the following events:
- skeletal-related events (pathological fractures, compression of the spinal cord or requirement of a 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, AEs)", "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)" and "general disorders and administration site conditions (SOC, severe AEs CTCAE grade ≥ 3)", "injury, poisoning and procedural complications (SOC, SAEs)".

c: Incomplete observations for potentially informative reasons at different periods of consideration of recordings or different observation periods; see Section 2.7.4.2 of the full dossier assessment

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

The risk of bias of the results for the outcome "overall survival" was rated as low in the SPARTAN study. This concurs with the company's assessment.

Concurring with the company, the risk of bias of the results for the outcome "symptomatic progression" was also rated as low.

The risk of bias of the results of the outcomes "health status (EQ-5D VAS)" and "health-related quality of life (FACT-P)" was rated as high due to incomplete observations for potentially

informative reasons (see Section 2.7.4.2 of the full dossier assessment). This assessment deviates from that of the company, which rated the risk of bias of the results of both outcomes as potentially low.

The outcomes of the category “side effects” were observed up to 28 days after the end of treatment. The differing treatment durations described before and the related differences in the observation periods between the study arms, chiefly explained by differences in the progression events, resulted in incomplete observations for potentially informative reasons. The risk of bias was therefore assessed as high for the results of the outcomes “SAEs”, “severe AEs (CTCAE grade ≥ 3)” and all specific AEs.

The risk of bias was rated as low for the outcome “discontinuation due to AEs”. The company assessed the risk of bias as high for the results of this outcome.

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 event time analyses are found in Appendix A of the present dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT

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]; p-value[a]**
SPARTAN					
Mortality					
overall survival	806	NA 62 (7.7)	401	39.03 [39.03; NC] 42 (10.5)	0.70 [0.47; 1.04]; 0.076
Morbidity					
symptomatic progression	806	NA 64 (7.9)	401	NA [36.83; NC] 63 (15.7)	0.45 [0.32; 0.63]; < 0.001
skeletal-related events (pathological fractures, compression of the spinal cord or requirement of a surgical intervention or radiotherapy of the bone)	806	NA 25 (3.1)	401	NA 18 (4.5)	0.62 [0.34; 1.14]; 0.127
Pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy	806	NA 35 (4.3)	401	NA [36.83; NC] 28 (7.0)	0.56 [0.34; 0.92]; 0.022
clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy	806	NA 18 (2.2)	401	NA 24 (6.0)	0.34 [0.18; 0.62]; < 0.001

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (continued)

Study Outcome category Outcome	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]; p-value[a]
Health-related quality of life					
FACT-P					
Total score, deterioration[b] by ≥ 10 points	806	6.60 [5.55; 7.92] 498 (61.8)	401	8.38 [6.47; 12.91] 222 (55.4)	1.06 [0.90; 1.25]; 0.465
prostate-specific subscale (PCS), deterioration[b] by ≥ 3 points	806	3.84 [3.71; 4.70] 575 (71.3)	401	3.78 [2.86; 4.80] 266 (66.3)	0.98 [0.84; 1.14]
Physical well-being (PWB), deterioration[b] by ≥ 3 points	806	6.57 [5.55; 8.38] 488 (60.5)	401	7.43 [5.59; 11.10] 222 (55.4)	1.02 [0.87; 1.20]
Social/familiar well-being (SWB), deterioration[b] by ≥ 3 points	806	7.46 [5.59; 11.07] 437 (54.2)	401	4.90 [3.84; 8.38] 218 (54.4)	0.88 [0.75; 1.04]
Emotional well-being (EWB), deterioration[b] by ≥ 3 points	806	12.98 [10.87; 18.43] 411 (51.0)	401	14.75 [10.61; NC] 176 (43.9)	1.08 [0.90; 1.29]
Functional well-being (FWB), deterioration[b] by ≥ 3 points	806	4.63 [3.78; 5.59] 522 (64.8)	401	6.51 [4.70; 9.26] 224 (55.9)	1.17 [1.00; 1.37]
Side effects					
AEs (additional information)	803	0.56 [0.46; 0.72] 775 (96.5)	398	0.76 [0.53; 0.92] 371 (93.2)	–
SAEs (without lethal AEs[c])	803	NA 199 (24.8)	398	35.25 [30.00; NC] 92 (23.1)	0.79 [0.61; 1.01]; 0.064
severe AEs (CTCAE grade ≥ 3)	803	22.44 [17.68; 26.18] 366 (45.6)	398	24.15 [18.53; 30.00] 137 (34.4)	1.13 [0.92; 1.37]; 0.246
Discontinuation due to AEs	803	NA 85 (10.6)	398	36.83 [36.83; NC] 28 (7.0)	1.33 [0.87; 2.04]; 0.193

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (continued)

Study Outcome category Outcome	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]; p-value[a]
Arthralgia (PT, AEs)	803	NA 126 (15.7)[d]	398	NA 30 (7.5)	1.80 [1.21 2.69]; 0.004
Skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)	803	NA 50 (6.2)	398	NA 1 (0.3)	23.48 [3.24; 170.03]; 0.002
Nervous system disorders (SOC, AEs)	803	NA 288 (35.9)	398	NA [26.28; NC] 90 (22.6)	1.53 [1.21; 1.94]; < 0.001
Renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)	803	NA 38 (4.7)	398	NA 39 (9.8)	0.37 [0.23; 0.58]; < 0.001
Hypothyroidism (PT, AEs)	803	NA 49 (6.1)	398	NA 5 (1.3)	4.09 [1.63; 10.30]; 0.003
General disorders and administration site conditions (SOC, severe AEs, CTCAE grade ≥ 3)	803	NA 18 (2.2)	398	NA 1 (0.3)	7.79 [1.04; 58.49]; 0.046
Injury, poisoning and procedural complications (SOC, SUEs)	803	NA 41 (5.1)	398	NA 5 (1.3)	3.05 [1.20; 7.75]; 0.019

a: HR, CI and p-value: Cox proportional hazards model; stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).
b: Deterioration means decrease in score by the respective MID.
c: Under consideration of lethal AEs, 204 (25.4%) vs. 93 (23.4%) patients experienced an SAE; event time analyses are not available.
d: According to the study report, 128 (15.9%) of the patients in the apalutamide arm had at least 1 event.
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: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PSADT: PSA doubling time; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

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

Study Outcome category	Apalutamide + ADT			Placebo + ADT			Apalutamide + ADT vs. placebo + ADT
Outcome	N[a]	Values at baseline mean (SD)	Change cycle 13 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change cycle 13 mean[b] (SE)	MD [95% CI][b]; p-value
SPARTAN							
Morbidity							
Health status (EQ-5D VAS[c, d])	ND	76.17 (17.31)	0.44 (0.55)	ND	76.81 (16.88)	−0.60 (0.88)	1.04 [ND]; < 0.315

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: Mean and SE (change cycle 13 per treatment group) as well as MD and p-value (group comparison): MMRM.
c: Representation of the results on cycle 13 (corresponds to approx. 1 year after start of treatment). This time point was chosen, because after that time point the proportion of patients with available questionnaire in relation to the randomized patients minus the patients who died in the placebo arm was too small. The study report includes results for all documentation time points up to cycle 29. The results are statistically significant for the time points "cycle 21" and "cycle 25", each in favour of apalutamide. However, at these analyses time points, completed questionnaires were only available for 45.5% and 22.0% or 33.6% and 14.2% of the patients in the apalutamide and the placebo arm.
d: Higher values indicate better health status; a positive group difference corresponds to an advantage of apalutamide.
ADT: androgen deprivation therapy; CI: confidence interval; EQ-5D European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications can be derived for the outcomes "overall survival", "symptomatic progression" and "discontinuation due to adverse events". There was a high risk of bias for all other outcomes; for the specific outcomes, however, the certainty of conclusions of the results was not always downgraded (see description of the results below).

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

In addition to the results for the outcome "overall survival", the company presented data on the validation of MFS as surrogate outcome for the outcome "overall survival". From the joint consideration of the results of the outcomes "overall survival" and "MFS", the company derived a hint of an added benefit for the outcome category "mortality". However, the data on the validation are unsuitable to show the validity of MFS as surrogate outcome for "overall survival" in the present therapeutic indication. In the benefit assessment, MFS was therefore

not considered to be a valid surrogate for "overall survival" (see Section 2.7.9.4 of the full dossier assessment).

Morbidity

Symptomatic progression

The outcome "symptomatic progression" is a combined outcome that includes the following events:

- development of a skeletal-related event (pathological fractures, compression of the spinal cord or requirement of a surgical intervention or radiotherapy 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.

A statistically significant difference between the treatment arms in favour of apalutamide + ADT in comparison with placebo + ADT was shown for the outcome "symptomatic progression". This resulted in an indication of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT.

Recording of the outcome "symptomatic progression" in the SPARTAN study is appreciated. However, the chosen operationalization of this outcome is unsuitable for extensive recording of the pain progression or the progression of other disease-related symptoms. Connection of the symptoms with the initiation of a systemic treatment, as it was done in the study, was insufficient for a sensitive recording of the events involved in symptomatic progression. It must be assumed that symptomatic progression of the disease occurred in the SPARTAN study without resulting in a change of the systemic anticancer treatment. Patients with symptomatic progression of the disease who decided against a new systemic therapy, but opted for supportive, symptom-alleviating treatment (e.g. escalation or initiation of a pain therapy with opioids) were not recorded here. It is unclear whether and how effect estimation would change when the events of the progression not connected with the systemic treatment had also been recorded (see also Section 2.7.4.3.2 of the full dossier assessment). Therefore, the extent of added benefit cannot be quantified for the outcome "symptomatic progression".

The company also derived an indication of an added benefit.

Health status (EQ-5D VAS)

Based on the mean differences, no statistically significant difference between the treatment arms was shown for the outcome "health status measured with the EQ-5D VAS". This resulted in no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT; an added benefit is therefore not proven.

The assessment of added benefit concurs with the company's assessment, which derived no added benefit on the basis of event time analyses (in each case time to improvement and time to deterioration by ≥ 7 or ≥ 10 points).

Health-related quality of life

The outcome "health-related quality of life" was recorded using the FACT-P. No statistically significant difference between the treatment arms was shown for "time to deterioration" in the FACT-P total score. This resulted in no hint of an added benefit of apalutamide + ADT in comparison with watchful waiting + ADT for the outcome "health-related quality of life"; an added benefit is therefore not proven.

The assessment of added benefit concurs with the company's assessment, which derived no added benefit on the basis of event time analyses on both deterioration and improvement.

Side effects

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

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs". Hence, for these outcomes there was no hint of greater or lesser harm from apalutamide + ADT in comparison with watchful waiting + ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

Severe AEs (CTCAE grade ≥ 3): skin and subcutaneous tissue disorders (SOC), general disorders and administration site conditions (SOC)

A statistically significant difference to the disadvantage of apalutamide + ADT in comparison with placebo + ADT was found for the outcomes "disease of the skin and subcutaneous tissue disorders (SOC)" and "general disorders and administration site conditions (SOC)" (in each case severe AEs [CTCAE grade ≥ 3]).

Due to the high risk of bias, this resulted in a hint of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT for the outcome "general disorders and administration site conditions".

Despite the high risk of bias, a high certainty of conclusions was assumed for the outcome "skin and subcutaneous tissue disorders" due to the effect size, and an indication of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT was derived.

The assessment of the added benefit deviates from the company's assessment, which presented the results on these outcomes, but derived no greater harm.

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

A statistically significant difference in favour of apalutamide + ADT in comparison with placebo + ADT was shown for the outcome "renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of lesser harm from apalutamide + ADT in comparison with watchful waiting + ADT. However, it is overall questionable whether the effect must actually be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the diseases. The events occurring under the SOC comprised typical locoregional symptoms of prostate cancer, e.g. urinary retention or hydronephrosis.

This assessment deviates from that of the company, which presented the results on the outcome, but derived no lesser harm.

SAEs: Injury, poisoning and procedural complications (SOC)

A statistically significant difference to the disadvantage of apalutamide + ADT in comparison with placebo + ADT was shown for the outcome "injury, poisoning and procedural complications (SOC, SAE)". This resulted in a hint of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT.

This deviates from the assessment of the company, which presented the results on this outcome, but did not use them for the derivation of the added benefit.

AEs: arthralgia (PT), nervous system disorders (SOC), hypothyroidism (PT)

A statistically significant difference to the disadvantage of apalutamide + ADT in comparison with placebo + ADT was shown for the outcomes "arthralgia (PT)", "nervous system disorders (SOC)" and "hypothyroidism (PT)" (in each case AEs). This resulted in a hint of greater harm from apalutamide + ADT in comparison with watchful waiting + ADT.

This assessment deviates from that of the company. It presented the results for these outcomes, but derived no greater harm.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 65 years/≥ 65 years to < 75 years/≥ 75 years)
- region (North America/Europe/rest of the world)
- PSADT (≤ 6 months/> 6 months)
- presence of a locoregional disease (N0 vs. N1)

The characteristics mentioned above were predefined for the outcomes "MFS" and "overall survival".

Subgroup analyses were available for all outcomes except for the outcome “health status (EQ-5D VAS, analysed)” and the outcomes on specific AEs.

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

Effect modifications cannot be derived from the available subgroup results.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for outcomes on morbidity and side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. Assessment is described hereinafter:

The outcome “symptomatic progression” was allocated to the category “serious/severe symptoms/late complications”.

The specific AEs “arthralgia”, “nervous system disorders” and “hypothyroidism” are each outcomes of the category “non severe/non serious side effects”, because most of the events included in these outcomes were non-serious/non-severe. The further specific AEs “skin and subcutaneous tissue disorders”, “renal and urinary disorders”, “general disorders and administration site conditions” as well as “injury, poisoning and procedural complications” were allocated to the category “severe/serious side effects”.

Table 16: Extent of added benefit at outcome level: apalutamide + ADT vs. watchful waiting + ADT

Outcome category **Outcome**	**Apalutamide + ADT vs. placebo + ADT** **Median time to event (months) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 39.03 HR: 0.70 [0.47; 1.04]; p = 0.076	lesser benefit/added benefit not proven
Morbidity		
Symptomatic progression	NA vs. NA HR: 0.45 [0.32; 0.63]; p < 0.001 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 requirement of a surgical intervention or radiotherapy of the bone)	NA vs. NA HR: 0.62 [0.34; 1.14]; p = 0.127	
Pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy	NA vs. NA HR: 0.56 [0.34; 0.92]; p = 0.022	
Clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy	NA vs. NA HR: 0.34 [0.18; 0.62]; p < 0.001	
Health status (EQ-5D VAS)	change: 0.44 vs. −0.60 MD: 1.04 [ND]; p = 0.315	lesser benefit/added benefit not proven
Health-related quality of life		
recorded with FACT-P total score		
Time to deterioration by ≥ 10 points	6.60 vs. 8.38 HR:1.06 [0.90; 1.25]; p = 0.465	lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: apalutamide + ADT vs. watchful waiting + ADT (continued)

Outcome category **Outcome**	**Apalutamide + ADT vs. placebo + ADT** **Median time to event (months) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs[d]	NA vs. 35.25 HR: 0.79 [0.61; 1.01]; p = 0.064	greater/lesser harm not proven
severe AEs (CTCAE grade ≥ 3)	22.44 vs. 24.15 HR: 1.13 [0.92; 1.37]; p = 0.246	greater/lesser harm not proven
discontinuation due to AEs	NA vs. 36.83 HR: 1.33 [0.87; 2.04]; p = 0.193	greater/lesser harm not proven
arthralgia (PT, AEs)	NA vs. NA HR: 1.80 [1.21; 2.69]; HR[e]: 0.56 [0.37; 0.83]; p = 0.004 probability: "hint"	outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 23.48 [3.24; 170.03]; HR[e]: 0.04 [0.01; 0.31]; p = 0.002 probability: "indication"[f]	outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
nervous system disorders (SOC, AEs)	NA vs. NA HR: 1.53 [1.21; 1.94]; HR[e]: 0.65 [0.52; 0.83]; p < 0.001 probability: "hint"	outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 0.37 [0.23; 0.58]; p < 0.001 probability: "hint"	outcome category: serious/severe side effects[g] $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
hypothyroidism (PT, AEs)	NA vs. NA HR: 4.09 [1.63; 10.30]; HR[e]: 0.24 [0.10; 0.61]; p = 0.003 probability: "hint"	outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
general disorders and administration site conditions (SOC, severe AEs, CTCAE grade ≥ 3)	NA vs. NA HR: 7.79 [1.04; 58.49]; HR[e]: 0.13 [0.02; 0.96]; p = 0.046 probability: "hint"	outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
injury, poisoning and procedural complications (SOC, SUEs)	NA vs. NA HR: 3.05 [1.20; 7.75]; HR[e]: 0.33 [0.13; 0.83]; p = 0.019 probability: "hint"	outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: apalutamide + ADT vs. watchful waiting + ADT (continued)

Outcome category **Outcome**	**Apalutamide + ADT vs. placebo + ADT** **Median time to event (months) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
a: Probability provided if there is a statistically significant and relevant effect. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: The operationalization of this outcome is unsuitable for an extensive recording of the pain progression or the progression of other disease-related symptoms. The effects of the potentially unrecorded events on the extent of added benefit are unclear. d: Without lethal AEs. Under consideration of lethal AEs, 204 (24.8%) vs. 93 (23.4%) patients experienced an SAE; event time analyses are not available. e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit. f: Despite the high risk of bias, the certainty of results was not downgraded due to the size of the effect. It is questionable whether the effect must actually be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the disease. ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MD: mean difference; NA: not achieved; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus		

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of apalutamide + ADT compared with watchful waiting + ADT

Positive effects	**Negative effects**
serious/severe symptoms/late complications: ▪ symptomatic progression: indication of added benefit – extent: "non-quantifiable"	serious/severe side effects: ▪ skin and subcutaneous tissue disorders (severe AEs): indication of greater harm – extent: "major" ▪ general disorders and administration site conditions (severe AEs): hint of greater harm – extent: "minor" ▪ injury, poisoning and procedural complications (SAEs): hint of greater harm - extent: "considerable"
serious/severe side effects[a]: ▪ renal and urinary disorders (severe AEs): hint of lesser harm – extent: "major"	non-serious/non-severe side effects: ▪ arthralgia (AEs): hint of greater harm - extent: "minor" ▪ nervous system disorders (AEs): hint of greater harm – extent: "minor" ▪ hypothyroidism (AEs): hint of greater harm - extent: "considerable"
a: It is questionable whether the effect must actually be allocated to the outcome category "side effects" or whether it rather reflects the symptoms of the disease. ADT: androgen deprivation therapy; AE: adverse event	

In the overall consideration, there was an indication of non-quantifiable added benefit in the outcome category “morbidity” and a hint of lesser harm regarding side effects with the extent “major” on the positive side. However, it is questionable whether the positive effect for the outcome “renal and urinary disorders” actually had to be allocated to the outcome category “side effects” or whether it rather reflected the symptoms of the disease. Clear demarcation is not possible on the basis of the available information.

The positive effects were offset by one indication and several hints of negative effects in the outcome category “side effects”, partly with major and considerable extents. However, these negative effects did not completely offset the positive effects, some of which achieved a major extent.

In the overall consideration of the results, there is an indication of considerable added benefit of apalutamide in comparison with the ACT “watchful waiting while maintaining ongoing conventional ADT” for patients with nmCRPC and a high risk of developing metastases.

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

Table 18: Apalutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with nmCRPC 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 ACT specified by the G-BA. b: Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone		

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

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

2.6 List of included studies

Aragon Pharmaceuticals. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer [online]. In: EU Clinical Trials Register. [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004322-24.

Aragon Pharmaceuticals. A study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer (SPARTAN): study details [online]. In: ClinicalTrials.gov. 07.02.2019 [Accessed: 15.02.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT01946204.

Aragon Pharmaceuticals. A study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer (SPARTAN): study results [online]. In: ClinicalTrials.gov. 07.02.2019 [Accessed: 15.02.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01946204.

Janssen Pharmaceutical. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer [online]. In: JAPIC Clinical Trials Information. 07.12.2016 [Accessed: 15.02.2019]. URL: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-163123.

Janssen Research & Development. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer: selective prostate AR targeting with ARN-509 (SPARTAN); study ARN-509-003; clinical study report [unpublished]. 2017.

Janssen Research & Development. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer: SPARTAN (selective prostate AR targeting with ARN-509); study ARN-509-003; clinical study protocol [unpublished]. 2017.

Janssen Research & Development. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer: SPARTAN (selective prostate AR targeting with ARN-509); study ARN-509-003; statistical analysis plan [unpublished]. 2017.

Janssen Research & Development. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer: SPARTAN (selective prostate AR targeting with ARN-509); study ARN-509-003; patient reported outcomes statistical analysis plan [unpublished]. 2017.

Janssen Research & Development. A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer: selective prostate AR targeting with ARN-509 (SPARTAN); study ARN-509-003; Zusatzanalysen [unpublished]. 2018.

Saad F, Cella D, Basch E, Hadaschik BA, Mainwaring PN, Oudard S et al. Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2018; 19(10): 1404-1416.

Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378(15): 1408-1418.

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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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