IQWiG Reports – Commission No. A20-20

Apalutamide (prostate cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Apalutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 May 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

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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
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
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)
mHSPC	metastatic hormone-sensitive prostate cancer
PFS	progression-free survival
PSA	prostate-specific antigen
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
WHO-PS	World Health Organization Performance Status

2 Benefit assessment

2.1 Extract of dossier 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 25 February 2020.

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

Research question

The aim of this report is to assess the added benefit of apalutamide in combination with androgen deprivation therapy (ADT) in comparison with the appropriate comparator therapy (ACT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

Table 2 presents 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

Therapeutic indication	**ACT[a]**
In adult men for the treatment of mHSPC in combination with ADT	▪ Only for patients with distant metastases (stage M1) who are in good general health (ECOG-PS/WHO-PS 0 to 1 or Karnofsky index ≥ 70%): conventional ADT[b] in combination with docetaxel[c] and prednisone or prednisolone or[d] ▪ Only for patients with newly diagnosed high-risk metastatic hormone-sensitive prostate cancer: conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. In the present therapeutic indication, conventional ADT is understood to mean surgical castration or medical castration using GnRH agonists or GnRH antagonists.
c. In the present therapeutic indication, patients are assumed to be eligible for combination therapy – additional conventional androgen deprivation therapy – with regard to their comorbidities and health status.
d. The listed therapies are ACTs for the respective listed subpopulation. The subpopulations overlap. Only for this overlapping set of patients do docetaxel + prednisolone or prednisone + ADT as well abiraterone acetate + prednisolone or prednisone + ADT represent ACTs ("OR-operation").

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer; WHO-PS: World Health Organization Performance Status

While the patient populations defined on the basis of the ACT in Table 2 are not completely disjunct, they do not fully overlap. The overlapping set of these patient populations comprises patients with mHSPC and the following disease characteristics: good general health (Eastern Cooperative Oncology Group Performance Status [ECOG-PS] / World Health Organization Performance Status [WHO-PS] of 0 to 1 or Karnofsky index ≥ 70%), high-risk prostate cancer, newly diagnosed prostate cancer. Only to patients of this overlapping set do both listed ACT options apply.

The company chose conventional ADT in combination with docetaxel as the ACT for the entire population of patients with mHSPC. It made no reference to prednisone or prednisolone.

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.

Results

Study pool of the company

The company presented an adjusted indirect comparison for the assessment of apalutamide + ADT versus docetaxel + ADT via the common comparator of placebo + ADT or ADT. The study pool of the company comprises the following RCTs:

- Intervention: apalutamide + ADT versus placebo + ADT: TITAN study
- Comparator therapy: docetaxel (+ prednisolone) + ADT versus ADT: STAMPEDE, GETUG, CHAARTED studies

The studies GETUG and CHAARTED, which were presented by the company with regard to the comparator therapy, are unsuitable for assessing the added benefit of apalutamide since they did not implement the ACT.

In the GETUG RCT, the intervention arm received docetaxel + ADT with dexamethasone as concomitant treatment for a maximum of 9 cycles. In all, study participants received a median of 8 cycles of docetaxel. However, according to the Summary of Product Characteristics (SPC), docetaxel is to be administered for a maximum of 6 cycles in patients with mHSPC. Further, unlike specified for the ACT, the GETUG study did not involve concomitant prednisone or prednisolone therapy. In total, the treatment with docetaxel + ADT used in the GETUG intervention arm does not reflect the specified ACT.

In the CHAARTED RCT, the intervention arm did not receive prednisone or prednisolone alongside docetaxel treatment (maximum of 6 cycles; + dexamethasone). The treatment used in the CHAARTED intervention arm therefore does not reflect the ACT.

Study pool of this assessment

Since only 1 RCT with apalutamide + ADT is available in the relevant therapeutic indication and this RCT used placebo + ADT as a comparator, only ADT is a suitable common comparator for an adjusted indirect comparison; this concurs with the company's view.

The study pool for the adjusted indirect comparison in the present assessment comprises the TITAN study on the apalutamide + ADT side and the STAMPEDE study on the docetaxel + prednisolone + ADT side.

Study design

TITAN (study with apalutamide + ADT)

TITAN is a double-blind, randomized study comparing apalutamide in combination with ADT versus placebo + ADT. Included were adult men with mHSPC who exhibited metastases in the form of ≥ 1 confirmed bone lesion(s). Patients had to be in good general health as measured by an ECOG-PS score of 0 or 1. Included patients had to have either undergone surgical castration or have started medical ADT with gonadotropin-releasing hormone (GnRH) analogues ≥ 14

days and ≤ 3 months before randomization. Apalutamide treatment was administered in accordance with its regulatory approval status in Germany.

The TITAN study started in 2015 and is still ongoing.

STAMPEDE (study with docetaxel + prednisolone + ADT)

The STAMPEDE study is a randomized, open-label, multi-arm, multi-stage platform study comparing various systemic drugs (12 arms in total) in patients with advanced or metastatic prostate cancer.

The STAMPEDE study included adult men with hormone-sensitive prostate cancer who were intended for long-term ADT and whose clinical picture corresponded to one of the 3 following criteria:

1) Newly diagnosed with distant metastases or lymph node metastases
2) Newly diagnosed with high-risk, locally advanced prostate cancer without distant metastases or lymph node metastases
3) Recurrent locally advanced or metastatic disease with prior radiotherapy and/or surgery

For the present benefit assessment, solely the parallel-group comparison between the docetaxel + prednisolone + ADT arm (Arm C) and the ADT arm (Arm A) is of relevance. However, only a subpopulation of each of these two study arms is relevant for the present benefit assessment (a detailed description of the relevant patient population follows below).

Docetaxel treatment in the intervention arm of the STAMPEDE study is administered in accordance with the docetaxel SPC for the present therapeutic indication. Both study arms allow both surgical ADT or medical ADT using GnRH analogues.

The STAMPEDE study started in 2005 and is ongoing.

Relevant patient population of the STAMPEDE study

Both patients with distant metastases and patients with locally advanced prostate cancer were included in the STAMPEDE study. Regardless of their metastatic status, all patients in the study had hormone-sensitive prostate cancer. In accordance with the regulatory approval of apalutamide, only the subpopulation of patients with hormone-sensitive prostate cancer and distant metastases is relevant for the present benefit assessment.

The company presented a STAMPEDE subpopulation which only includes patients with distant metastases.

Overall, the STAMPEDE subpopulation presented by the company sufficiently reflects the target population of the present assessment and is included in the present benefit assessment (below referred to as “relevant subpopulation”).

Similarity of studies for the indirect comparison

All things considered, the study designs and included patient populations of TITAN and STAMPEDE are deemed sufficiently similar for conducting an adjusted indirect comparison via the common comparator of placebo + ADT and ADT, respectively. Differences exist, however, concerning the outcome of skeletal-related events; consequently, no adjusted indirect comparison was conducted for this outcome.

Risk of bias

The risk of bias across outcomes was rated as low for TITAN and STAMPEDE.

On the outcome level, a low risk of bias was found in the TITAN study for results on overall survival, morbidity, and discontinuation due to AEs. For the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3), there is a high risk of bias.

For the STAMPEDE study, a low risk of bias was found for all outcomes included in the assessment.

Results

Mortality

Overall survival

For the outcome of overall survival, the adjusted indirect comparison shows no statistically significant difference between apalutamide + ADT and docetaxel + prednisolone + ADT. Consequently, there is no hint of added benefit of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; an added benefit is therefore not proven.

In addition to presenting results on the outcome of overall survival, the company's dossier offers data for validating radiographic progression-free survival (rPFS) as a surrogate for the outcome of overall survival. However, the validation data are unsuitable for demonstrating the validity of rPFS as a surrogate for overall survival in the present therapeutic indication. In the benefit assessment, rPFS is therefore not included as a valid surrogate for overall survival.

Morbidity

Skeletal-related events

The common comparator arms of the TITAN and STAMPEDE studies exhibit markedly different rates of patients with an event, thereby negating outcome-related similarity between the two studies. While both studies generally allowed drug-based prophylaxis of skeletal-related events, no data are available as to how many patients actually received concomitant treatment for skeletal-related events and which drugs were used.

Consequently, no data usable for an adjusted indirect comparison are available for the outcome of skeletal-related events. This does not result in a hint of added benefit; an added benefit is therefore not proven.

Health-related quality of life

Regarding the outcome of health-related quality of life, the TITAN and STAMPEDE studies used different instruments for recording the outcome; hence, no usable data for an indirect comparison are available. Consequently, there is no hint of added benefit of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; an added benefit is therefore not proven.

Adverse events

SAEs

On the apalutamide + ADT side of the adjusted indirect comparison, the only available result for the outcome of SAEs is from one study (TITAN) with a high risk of bias at the outcome level. At first sight, the prerequisites are therefore not met for deriving any conclusions of adequate certainty of results on added benefit from an adjusted indirect comparison. For this outcome, however, both the STAMPEDE study and the adjusted indirect comparison via the common comparator of placebo + ADT or ADT show a large effect estimation. In view of the available data, the advantage found in the adjusted indirect comparison is unlikely to be fully negated by potential bias. Hence, despite the high risk of bias at outcome level in the TITAN study, the qualitative certainty of results is sufficiently high to allow interpretation of the present effect. Consequently, in the present situation, it is possible to derive a hint of greater or lesser harm of apalutamide + ADT.

The adjusted indirect comparison for the outcome of SAEs shows a marked statistically significant difference in favour or apalutamide + ADT in comparison with docetaxel + prednisone + ADT. Given the data constellation in the STAMPEDE study, the above conclusion applies to the period of 6 to 7 months from randomization. This results in a hint of lesser harm of apalutamide + ADT. However, the effect size cannot be quantified due to the present data constellation.

Severe AEs (CTCAE grade ≥ 3)

For the results on the outcome of severe AEs (CTCAE grade ≥ 3), there is a high risk of bias in the TITAN study. Hence, any effect estimation for the indirect comparison regarding this outcome is not sufficiently reliable.

For the outcome of severe AEs (CTCAE grade ≥ 3), there is therefore no hint of greater or lesser harm of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; therefore, there is no proof of greater or lesser harm.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, data are available only for the intervention side of the indirect comparison. Consequently, there is no hint of greater or lesser harm of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; greater or lesser harm is therefore not proven.

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 added benefit of the drug apalutamide in comparison with the ACT are assessed as follows:

All things considered, the results show an exclusively positive effect for apalutamide + ADT in the category of adverse events.

In summary, for patients with mHSPC who are in good general health, there is a hint of non-quantifiable added benefit of apalutamide in comparison with conventional ADT in combination with docetaxel and prednisone or prednisolone.

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

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

Table 3: Apalutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
In adult men for the treatment of mHSPC in combination with ADT	▪ Only for patients with distant metastases (stage M1) who are in good general health (ECOG-PS/WHO-PS 0 to 1 or Karnofsky index ≥ 70%): conventional ADT in combination with docetaxel and prednisone or prednisolone or[d] ▪ Only for patients with newly diagnosed high-risk metastatic hormone-sensitive prostate cancer: conventional ADT in combination with abiraterone acetate and prednisone or prednisolone	Hint of non-quantifiable added benefit [b, c]

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the TITAN study. The STAMPEDE study allowed the inclusion of patients with a WHO-PS of 2. However, the majority of patients had a WHO-PS of 0. No specific data are available on the number of patients with a WHO-PS of 2. The conclusion on added benefit therefore applies to patients in good general health (with ECOG-PS / WHO-PS 0–1).
c. Patients with brain metastases were excluded from the TITAN and STAMPEDE studies. It remains unclear whether the observed effects translate to patients with brain metastases.
d. The listed therapies are ACTs for the respective listed subpopulation. The subpopulations overlap. Only for this overlapping set of patients do docetaxel + prednisolone or prednisone + ADT as well abiraterone acetate + prednisolone or prednisone + ADT represent ACTs ("OR-operation").

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; mHSPC: metastatic hormone-sensitive prostate cancer; WHO-PS: World Health Organization Performance Status

The approach for deriving an overall conclusion on 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 any added benefit of apalutamide in combination with ADT in comparison with the ACT in patients with mHSPC.

Table 4 presents 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

Therapeutic indication	**ACT[a]**
In adult men for the treatment of mHSPC in combination with ADT	▪ Only for patients with distant metastases (stage M1) who are in good general health (ECOG-PS/WHO-PS 0 to 1 or Karnofsky index ≥ 70%): conventional ADT[b] in combination with docetaxel[c] and prednisone or prednisolone or[d] ▪ Only for patients with newly diagnosed high-risk metastatic hormone-sensitive prostate cancer: conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. In the present therapeutic indication, conventional ADT is understood to mean surgical castration or medical castration using GnRH agonists or GnRH antagonists.
c. In the present therapeutic indication, patients are assumed to be eligible for combination therapy – additional conventional androgen deprivation therapy – with regard to their comorbidities and health status.
d. The listed therapies are ACTs for the respective listed subpopulation. The subpopulations overlap. Only for this overlapping set of patients do docetaxel + prednisolone or prednisone + ADT as well abiraterone acetate + prednisolone or prednisone + ADT represent ACTs ("OR-operation").

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer; WHO-PS: World Health Organization Performance Status

While the patient populations defined on the basis of the ACT in Table 4 are not completely disjunct, they do not fully overlap. The overlapping set of these patient populations comprises patients with mHSPC with the following disease characteristics:

- Good general health (ECOG Performance Status [PS] / WHO-PS 0 to 1 or Karnofsky index ≥ 70%)
- High-risk prostate cancer
- Newly diagnosed prostate cancer

Only patients of this overlapping have both listed ACT options.

The company chose conventional ADT in combination with docetaxel as the ACT for the entire population of patients with mHSPC. It made no reference to prednisone or prednisolone. The effect of this deviation on the present assessment is described in Section 2.3.

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.

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: 27 December 2019)
- Bibliographic literature search on apalutamide (most recent search on 19 December 2019)
- Search in trial registries for studies on apalutamide (most recent search on 29 January 2020)
- Bibliographic literature search on the ACT (most recent search on 19 December 2019)
- Search in trial registries on the ACT (most recent search on 20 December 2019)

To check the completeness of the study pool:

- Search in trial registries for studies on apalutamide (most recent search on 13 March 2020)
- Focused search for systematic reviews on the ACT (most recent search on 19 March 2020)

The check did not identify any additional relevant studies.

Study pool of the company

The company presented an adjusted indirect comparison for the assessment of apalutamide + ADT versus docetaxel + ADT via the common comparator of placebo + ADT or ADT. The study pool of the company comprises the following RCTs:

- Intervention: apalutamide + ADT versus placebo + ADT: TITAN study
- Comparator therapy: docetaxel (+ prednisolone) + ADT versus ADT: STAMPEDE, GETUG, CHAARTED studies

The studies GETUG and CHAARTED, which were presented by the company with regard to the comparator therapy, are unsuitable for assessing the added benefit of apalutamide since they did not implement the ACT.

Failure to implement the ACT in the CHAARTED and GETUG studies

GETUG study (study with docetaxel + ADT)

The GETUG study [3-5] is an open-label, randomized, controlled study comparing docetaxel + ADT with ADT monotherapy in patients with metastatic prostate carcinoma. It included adult patients with histologically confirmed prostate cancer and an Eastern Cooperative Oncology Group (ECOG)-PS ≤ 2 or Karnofsky index $\geq 70\%$, for whom radiological confirmation of distant metastases was additionally available. Patients' ADT start date had to be no earlier than

2 months before study inclusion. Patients receiving chemotherapy for the treatment of metastases were excluded.

A total of 385 patients were randomized in a 1:1 ratio, 192 of them into the docetaxel + ADT arm and 193 into the ADT arm.

The study's intervention arm used docetaxel + ADT with concomitant dexamethasone treatment for a maximum of 9 cycles. Both the intervention arm and the comparator arm allowed ADT in the form of surgical castration or GnRH-agonist therapy, either alone or in combination with nonsteroidal antiandrogens, until the development of resistance.

The primary outcome was overall survival. Other outcomes were clinical/biochemical progression-free survival (PFS), morbidity, change in health-related quality of life, and adverse events (AEs).

Overall, study participants received a median of 8 cycles of docetaxel. This number of docetaxel treatment cycles is not covered by the regulatory approval. As per the SPC, docetaxel is to be administered for a maximum of 6 cycles in patients with mHSPC [6].

Further, in deviation from ACT specifications, the GETUG study did not involve concomitant prednisone or prednisolone therapy.

Overall, docetaxel + ADT as the therapy used in the GETUG intervention arm does not reflect the ACT specified by the G-BA. In deviation from the company, this assessment does not include the GETUG study.

CHAARTED study (study with docetaxel + ADT)

The CHAARTED study [7-11] is an open-label, randomized, controlled study comparing docetaxel + ADT versus ADT in patients with metastatic prostate cancer. Included were adult patients with either pathologically confirmed prostate cancer or a corresponding diagnosis on the basis of elevated prostate-specific antigen (PSA) levels who also exhibited radiological evidence of distant metastases and an ECOG-PS of ≤ 2. Patients who received ADT for the treatment of metastatic prostate cancer were included if treatment started a maximum of 120 days before randomization and no signs of disease progression had been found since that time.

A total of 790 patients were randomized in a 1:1 ratio, 397 of them into the docetaxel + ADT arm and 393 into the ADT arm.

In the study's intervention arm, docetaxel treatment was administered in accordance with its German approval status, using up to 6 cycles and concomitant dexamethasone therapy [6]. The study did not provide for accompanying treatment with prednisone or prednisolone. ADT in both CHAARTED study arms could be either surgical or medical using GnRH analogues until

the development of resistance. Any patients in the ADT arm who failed to respond to hormone therapy were allowed to switch to docetaxel therapy.

The primary outcome was overall survival. Other outcomes were time to clinical progression, time to castration-resistant prostate cancer, morbidity, as well as change in health-related quality of life and AEs.

As already described for the GETUG study, the CHAARTED study did not provide for any concomitant prednisone or prednisolone treatment alongside docetaxel. This does not correspond to the ACT, which specifies docetaxel in combination with prednisone or prednisolone to be administered alongside ADT. The therapy used in the intervention arm of the CHAARTED study therefore does not reflect the ACT. In deviation from the company, this assessment does not include the CHAARTED study.

2.3.1 Included studies

Since only 1 RCT with apalutamide is available in the relevant therapeutic indication and this RCT used placebo + ADT as a comparator, only placebo + ADT or ADT is a suitable common comparator for an adjusted indirect comparison; this concurs with the company's view.

The studies listed in Table 5 are included in this assessment.

Table 5: Study pool – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + 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])
Study with the intervention						
TITAN (NCT02489318)	Yes	Yes	No	No[d]	Yes [12]	Yes [13,14]
Study with the comparator therapy						
STAMPEDE (NCT00268476)	No	No	Yes	No	Yes [15]	Yes [16-21]

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; RCT: randomized controlled trial

However, the study pool for the benefit assessment diverges from that of the company (see Section 2.3).

Figure 1 schematically represents the indirect comparison.

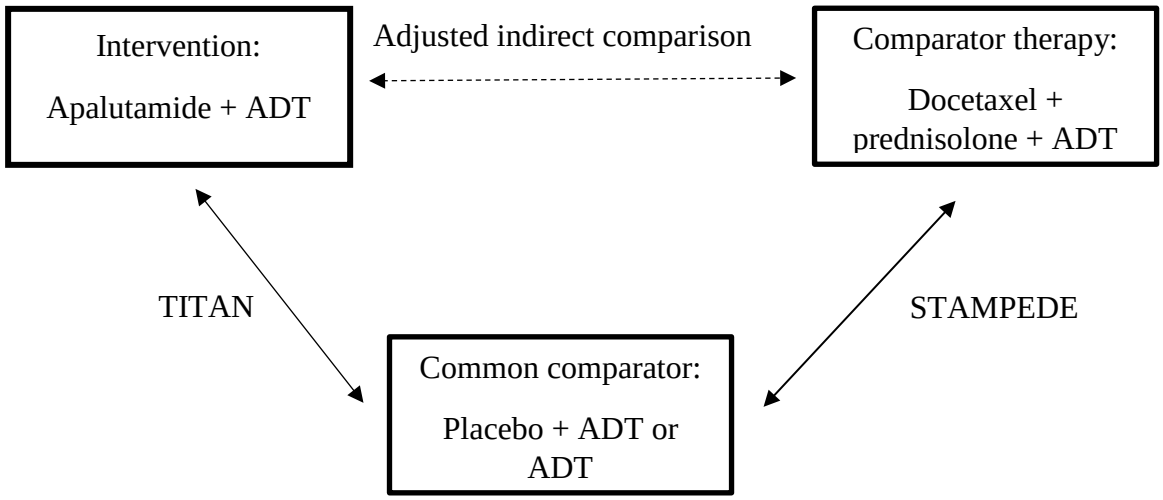

Figure 1: Study pool for the indirect comparison of apalutamide + ADT and the ACT of docetaxel + prednisolone + ADT

2.3.2 Study characteristics

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

Table 6: Characterization of the included studies – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
Study with the intervention						
TITAN	RCT, double-blind, parallel-group	Adult patients with mHSPC and an ECOG-PS of 0 or 1[c]	Apalutamide + ADT (N = 525) Placebo + ADT (N = 527)	Screening: until 28 days before randomization Treatment: until disease progression, withdrawal of informed consent, or unacceptable treatment-related toxicity[d] Follow-up: until death, consent withdrawal, lost to follow-up, or study end	260 centres in: Argentina, Australia, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, Israel, Japan, Mexico, Poland, Romania, Russia, South Korea, Spain, Sweden, Turkey, Ukraine, United Kingdom, USA 12/2015–ongoing Data cut-off date: 23/11/2018	Primary: Overall survival; rPFS Secondary: Morbidity, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
Study with the comparator therapy						
STAMPEDE	RCT, open-label, parallel-group	Adult patients with prostate cancer who were intended for long-term ADT[e], with WHO-PS 0–2: ▪ With newly diagnosed, metastatic or lymph-node-positive disease, or ▪ With high-risk, locally advanced, non-metastatic disease who are intended for radiotherapy or ▪ With prior radiotherapy or surgery, with recurrent, locally advanced, or metastatic disease	Arms relevant for assessment[f]: Docetaxel + prednisolone + ADT (N = 592) ADT (N = 1184) Relevant subpopulation thereof[g]: Docetaxel + prednisolone + ADT (n = 362) ADT (n = 724)	Screening: for up to 8 weeks Treatment: until disease progression, unacceptable toxicity, withdrawal of informed consent, start of new cancer therapy, or as decided by the physician ▪ Docetaxel: maximum of 6 cycles ▪ ADT: n.s. Follow-up: until death, withdrawal of informed consent	Total of 116 centres in the UK and Switzerland[h] Entire study: 09/2005–ongoing Relevant study arms: n.s. Data cut-off date (OS): 13/07/2018	Primary: Overall survival, failure-free survival Secondary: Morbidity, health-related quality of life, AEs

a. Data on primary outcomes were included irrespective of their relevance for this benefit assessment. Data on secondary outcomes were included only concerning available outcomes relevant for this benefit assessment.
b. Patients with brain metastases or exclusively visceral metastases were excluded.
c. Until Amendment 1, patients with an ECOG-PS of 2 were eligible for inclusion as well.
d. Following the interim analysis (data cut-off date of 23/11/2018), the study was unblinded as recommended by the IDMC, and patients from the control arm were allowed to switch to apalutamide in an extension phase.
e. According to guidelines, long-term ADT is a treatment option for patients with mHSPC [22].
f: The STAMPEDE study investigated a comparator arm (Arm A) and various intervention arms. The comparison between Arm A (ADT) and Arm C (docetaxel + prednisolone + ADT) is relevant for the present assessment.
g. Patients with metastatic prostate cancer.
h. No information is available on how many centres included patients in the 2 relevant study arms.

AE: adverse event; ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; IDMC: Independent Data and Safety Committee; mHSPC: metastatic hormone-sensitive prostate cancer; n: relevant subpopulation; N: number of randomized patients; n.s.: not specified; OS: overall survival; RCT: randomized controlled trial; rPFS: radiographic progression-free survival; WHO-PS: World Health Organization Performance Status

Table 7: Characterization of the intervention – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Study	Intervention / comparator therapy	Common comparator
Study with the intervention		
TITAN	Apalutamide 240 mg orally (4 x 60 mg tablets) daily + ADT[a]	Placebo orally (4 x 60 mg tablets) daily + ADT[a]
	Treatment modifications: ▪ Apalutamide: Treatment discontinuation in case of toxicity grade ≥ 3; in case of recurrent toxicity, a maximum of 2 dose reductions to 180 mg or 120 mg; treatment discontinuation in case of toxicity or grade 4 neurotoxicity persisting after reduction ▪ ADT: no modification	▪ ADT: no modification
	Prior treatment Allowed: ▪ In case of prior docetaxel treatment: maximum of 6 cycles, last dose ≤ 2 months before randomization, continued response as confirmed by imaging or PSA test ▪ Maximum of one radiotherapy / surgical intervention; radiotherapy of metastatic lesions must have been completed before randomization ▪ Prior treatment of local prostate cancer (all treatments must have been completed ≥ 1 year before randomization): ≤ 3 years of ADT in total or other treatment such as radiotherapy, prostatectomy, lymph node dissection, and systemic therapies Disallowed: ▪ Prior treatment with other, next-generation antiandrogens (e.g. enzalutamide), CYP17 inhibitors (e.g. abiraterone acetate), immunotherapy (e.g. sipuleucel-T), radiopharmaceuticals ▪ Surgical procedures other than castration, radiation, experimental drugs within 28 days before randomization **Concomitant treatment** Allowed: ▪ Bisphosphonate or denosumab for the treatment of bone metastases, at a stable dose ≥ 28 days before randomization, otherwise only after documented progression; also allowed for osteoporosis prevention ▪ Temporary use of opioids for pain management ▪ Surgical procedures or procedures treating local progression (e.g. transurethral prostate resection and use of urethral stents) ▪ Further supportive therapies, e.g. haematopoietic growth factors, transfusions Disallowed: ▪ Drugs known for lowering the seizure threshold (e.g. atypical antipsychotic drugs, tricyclic antidepressants) had to have been discontinued or substituted ≥ 28 days before randomization ▪ CYP17 inhibitors (e.g. abiraterone acetate), other hormone therapies for prostate cancer, other antiandrogens (e.g. enzalutamide, bicalutamide, nilutamide, flutamide, cyproterone acetate) ▪ Chemotherapy, cancer immunotherapy, other cancer drugs ▪ Experimental substances ▪ Radiotherapy for new painful metastases which were not present at the start of the study	

Table 7: Characterization of the intervention – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Study	Intervention / comparator therapy	Common comparator
Study with the comparator therapy		
STAMPEDE	Docetaxel 75 mg/m^2 i.v. on Day 1 of a cycle (maximum of six 21-day cycles) + ADT[b, c] + Prednisolone 5 mg twice daily + Dexamethasone both before and after the infusion	ADT[b, c]
	Treatment modifications: ▪ ADT: n.s. ▪ Docetaxel: 2 dose reductions down to a minimum of 45 mg/m^2 allowed due to toxicity	▪ ADT: n.s.
	Prior treatment Allowed: ▪ Up to 3 months of prior ADT (surgical castration or administration of LHRH analogues), with or without simultaneous administration of antiandrogens (the latter had to have already been started 14 weeks before randomization) Disallowed: ▪ Chemotherapy, surgery within 4 weeks before study inclusion ▪ Long-term hormone therapy ▪ Systemic therapy (except for the therapies mentioned below) **Concomitant treatment** Allowed: ▪ Any treatment deemed appropriate by the investigator (e.g. NSAIDs, bisphosphonates, vitamins) ▪ Antiandrogens to treat flare reaction[d] in LHRH agonist treatment	

a. Treatment with GnRH agonists or antagonists or surgical castration had to have started ≥ 14 days before randomization, and treatment duration had to have been ≤ 3 months (6 months for patients with prior docetaxel treatment). Patients who took a GnRH agonist ≤ 28 days before randomization had to take a 1st generation antiandrogen ≥ 14 days before randomization. The use of the antiandrogen had to have been discontinued before randomization.
b. Surgical castration or administration of GnRH agonists or antagonists.
c. Any ADT before study start should have started at most 12 weeks before randomization.
d. Short-term major increase in blood testosterone levels by the administration of GnRH agonists.

ADT: androgen deprivation therapy; CYP: cytochrome; GnRH: gonadotropin-releasing hormone; n.s.: not specified; NSAID: nonsteroidal anti-inflammatory drugs; RCT: randomized controlled trial

Study design

TITAN (study with apalutamide + ADT)

TITAN is a double-blind, randomized study comparing apalutamide in combination with ADT versus placebo + ADT. Included are adult men with mHSPC who exhibit metastases in the form of ≥ 1 confirmed bone lesion(s). Patients must be in good general health as measured by an

ECOG-PS score of 0 or 1. Included patients must have either undergone surgical castration or have started medical ADT with GnRH analogues ≥ 14 days and ≤ 3 months before randomization. Prior therapy with ≤ 6 cycles of docetaxel is permitted as well. Patients with prior docetaxel treatment are allowed to start ADT ≤ 6 months before study inclusion. Excluded are patients who exhibit exclusively visceral or lymph node metastases as well as those with brain metastases, cardiovascular or cerebrovascular diseases, or abnormal haematological, hepatic, or renal function.

In total, 1052 patients have been randomized in a 1:1 ratio to the two study arms. Stratification is done by Gleason score (< 7 versus ≥ 7), geographic region (North America and Europe versus all other countries), and prior docetaxel treatment (yes versus no).

Apalutamide treatment is administered in accordance with its German approval status [23]. Patients are treated with apalutamide until disease progression or unacceptable toxicity; thereafter, they are allowed to switch to a subsequent therapy.

At the available data cut-off date (23 November 2018), 16.6% of patients in the apalutamide + ADT arm and 36.1% of patients in the placebo + ADT arm already received subsequent systemic therapy. Most of these patients received hormone therapy, e.g. with an antiandrogen and/or chemotherapy (see Table 29 of the full dossier assessment).

Overall survival and rPFS are defined as coprimary outcomes. Other patient-relevant outcomes are symptomatic local progression (urethral or bladder outlet obstruction), pain, fatigue, skeletal-related events, health-related quality of life, health status, and AEs.

The TITAN study started in 2015 and is still ongoing. Following the interim analysis for the given data cut-off date (23 November 2018), the study was unblinded, and patients in the placebo + ADT arm were allowed to switch treatment to apalutamide + ADT.

STAMPEDE (study with docetaxel + prednisolone + ADT)

The STAMPEDE study is a randomized, open-label, multi-arm, multi-stage platform study comparing various systemic drugs (12 arms in total) in patients with advanced or metastatic prostate cancer.

The STAMPEDE study includes adult men with hormone-sensitive prostate cancer who are intended for long-term ADT and whose clinical picture corresponds to one of the 3 following criteria:

1) Newly diagnosed with distant metastases or lymph node metastases
2) Newly diagnosed with high-risk, locally advanced prostate cancer without distant metastases or lymph node metastases
3) Recurrent locally advanced or metastatic disease with prior radiotherapy and/or surgery

Excluded are patients with brain metastases, cardiovascular or cerebrovascular disease, abnormal haematological, hepatic, or renal function, or a World Health Organization Performance Status (WHO-PS) > 2.

For the present benefit assessment, solely the parallel-group comparison between the docetaxel + prednisolone + ADT arm (Arm C) and the ADT arm (Arm A) is of relevance. A total of 1776 patients were included in these study arms, 592 patients in the docetaxel + prednisolone + ADT arm and 1184 in ADT arm. However, only a subpopulation of each of these two study arms is relevant for the present benefit assessment (a detailed description of the relevant patient population follows below).

Docetaxel treatment in the STAMPEDE intervention arm is performed as shown in Table 7 and corresponds to the specifications of the docetaxel SPC in the present therapeutic indication [6]. ADT in both study arms can be either surgical or medical using GnRH analogues. In patients who have already received ADT when entering the study, ADT must have been ongoing for at least 14 days and no more than 3 months before study entrance.

According to the protocol, ADT in the relevant study arms is continued for at least 2 years or until the first radiological, clinical, or biochemical progression. Docetaxel treatment is performed for a maximum of 6 cycles or until disease progression, unacceptable toxicity, withdrawal of informed consent, start of new cancer therapy or the physician's decision to discontinue treatment.

Overall survival is the primary outcome for the STAMPEDE study arms relevant for the present assessment. Further patient-relevant outcomes are symptomatic skeletal-related events, other symptoms, health status, health-related quality of life, and AEs.

The STAMPEDE study started in 2005 and is ongoing. In the STAMPEDE study, patient recruitment differed in length for the individual study arms. For the docetaxel + prednisolone + ADT arm, patients were recruited between October 2005 and March 2013. For the available data cut-off date (13 July 2018), only patients recruited in this time period were analysed in the ADT arm as well.

Relevant patient population of the STAMPEDE study

Both patients with distant metastases and patients with locally advanced prostate cancer have been included in the STAMPEDE study. Regardless of their metastatic status, all patients in the study have hormone-sensitive prostate cancer. In accordance with the approval of apalutamide, only the subpopulation of patients with hormone-sensitive prostate cancer and distant metastases is relevant for the present benefit assessment.

The company presented a STAMPEDE subpopulation comprising only patients with distant metastases. It includes a total of 1086 patients, 362 patients in the docetaxel + prednisolone +

ADT arm and 724 in ADT arm. In total, the subpopulation comprises 61% of the total population included in the relevant arms of the STAMPEDE study.

The vast majority of patients in the relevant subpopulation has a WHO-PS of 0 (74.6% and 72%, respectively). For the remaining patients, a WHO-PS of 1 to 2 has been reported.

Overall, the STAMPEDE study subpopulation presented by the company sufficiently represents the target population of and is included in the present benefit assessment (this subpopulation is referred to as relevant subpopulation in the present assessment).

The majority of patients in the relevant subpopulation already received systemic follow-up therapy at the available data cut-off date (docetaxel + prednisolone + ADT arm: 68%, ADT arm: 80%). However, the available data do not show whether the information on subsequent therapy concerns only prostate cancer therapy or also includes concomitant therapies such as bisphosphonates (see Table 30 of the full dossier assessment). In the docetaxel + prednisolone + ADT arm, the subsequent therapy predominantly consisted of abiraterone and/or antiandrogens. In the ADT arm, the subsequent therapy was most commonly docetaxel and/or antiandrogens. However, even in the docetaxel + prednisolone + ADT arm, 14% of patients subsequently continued to receive docetaxel therapy (see Table 30 of the full dossier assessment).

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT

Study **Outcome category** **Outcome**	**Planned follow-up**
Study with the intervention	
TITAN	
Mortality	
Overall survival	Until death, withdrawal of informed consent, lost to follow-up, or study end
Morbidity	
Skeletal-related events	Until death, withdrawal of informed consent, lost to follow-up, or study end
Health-related quality of life	No data suitable for indirect comparison available[a]
Adverse events	Until 30 days after the last dose of the study medication
Study with the comparator therapy	
STAMPEDE	
Mortality	
Overall survival	Until death
Morbidity	
Skeletal-related events	Until death
Health-related quality of life	No data suitable for indirect comparison available[a]
Adverse events	Until 30 days after the last dose of the study medication
a. The studies used different instruments for measuring health-related quality of life (see Table 12).	
ADT: androgen deprivation therapy; RCT: randomized controlled trial	

The follow-up durations for AE outcomes were systematically shortened in the TITAN and STAMPEDE studies since they were recorded only for the period of treatment with the study drug (plus 30 days). To allow drawing reliable conclusions over the entire study period or until patient death, however, these outcomes – like survival – would have to have been measured and analysed over the entire study period.

Data cut-off dates

TITAN study

The TITAN study had a pre-specified final data cut-off in the form of an analysis of overall survival after the death of 410 patients. Amendment 4 (05 September 2018) specifies that 2 prior interim analyses on overall survival be conducted after the deaths of approximately 50% (205 patients) and approximately 70% (287 patients) of the above number of 410 patients. The analysis of the further outcomes was to be conducted at the time of the 1st interim analysis. The available 1st data cut-off (23 November 2018) took place after 200 patients died and therefore corresponds to the 1st interim analysis. This data cut-off supplies data for all patient-relevant

outcomes. The benefit assessment used this data cut-off. This concurs with the company's approach.

STAMPEDE study

For the STAMPEDE study, the company presented an analysis on the basis of the pre-defined data cut-off date of 13 July 2018 for use in the assessment of added benefit. No other data cut-offs have been published for the relevant comparison. For this data cut-off, data are available for all patient-relevant outcomes. The benefit assessment used this data cut-off. This concurs with the company's approach.

Study population

Table 9 shows the patient characteristics in the included studies.

Table 9: Characterization of the study populations – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

	Study with apalutamide + ADT		**Study with docetaxel + prednisolone + ADT**	
Study	**TITAN**		**STAMPEDE**	
Characteristics **Category**	**Apalutamide + ADT**	**Placebo + ADT**	**Docetaxel + prednisolone + ADT**	**ADT**
	N[a] = 525	**N[a] = 527**	**N[a] = 362**	**N[a] = 724**
Age [years], median [Q1; Q3]	69 [63; 75]	68 [62; 74]	65 [60; 70]	65 [60; 71]
Time from initial diagnosis to randomization [months], median [Q1; Q3]	4.1 [0.5; 222.9][b]	4.0 [0.7; 341.4][b]	2.4 [1.8; 3.1][c]	2.3 [1.6; 3.0][c]
Race/ethnicity, n (%)				
White	354 (67)	365 (69)	n.s.	n.s.
Black	10 (2)	9 (2)	n.s.	n.s.
Asian	119 (23)	110 (21)	n.s.	n.s.
Other	31 (6)[d]	35 (6)[d]	n.s.	n.s.
Unknown	11 (2)	8 (2)	n.s.	n.s.
Gleason score, n (%)				
< 8	174 (33.1)[e]	169 (32.1)[e]	65 (18)	158 (22)
≥ 8	351 (66.9)[e]	358 (67.9)[e]	253 (70)	480 (66)
Unknown	0 (0)	0 (0)	44 (12)	86 (12)
Region, n (%)				
North America / Europe	173 (33)	173 (33)	0 (0)	0 (0)
Europe	n.s.	n.s.	362 (100)	724 (100)
Rest of the world	352 (67)	354 (67)	0 (0)	0 (0)
ECOG-PS, n (%)				
0	328 (62.5)	348 (66.0)	270 (74.6)[f]	521 (72.0)[f]
1–2	197 (37.5)[e]	179 (34.0)[e]	92 (25.4)[f]	203 (28.0)[f]
1	197 (37.5)	178 (33.8)	n.s.	n.s.
2	0 (0)	1 (0.2)	n.s.	n.s.
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
Distant metastases at initial diagnosis, n (%)	411 (78.3)	441 (83.7)	347 (95.9[e])	690 (95.3[e])
Distant metastases at study start, n (%)	525 (100)	527 (100)	362 (100)[g]	724 (100)[g]
Localization of metastases at study start, n (%)				
Bone	525 (100.0)	527 (100.0)	307 (85)	634 (88)
Bone only	289 (55.0)	269 (51.0)	n.s.	n.s.
Lymph nodes	199 (37.9)	219 (41.6)	102 (28)	221 (31)
Visceral	56 (10.7)	72 (13.7)	n.s.	n.s.

Table 9: Characterization of the study populations – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

	Study with apalutamide + ADT		**Study with docetaxel + prednisolone + ADT**	
Study	**TITAN**		**STAMPEDE**	
Characteristics **Category**	**Apalutamide + ADT**	**Placebo + ADT**	**Docetaxel + prednisolone + ADT**	**ADT**
	N[a] = 525	**N[a] = 527**	**N[a] = 362**	**N[a] = 724**
Prior therapy				
Prostatectomy or radiotherapy	94 (17.9)	79 (15.0)	n.s.	n.s.
Prostatectomy	26 (5.0)	27 (5.1)	n.s.	n.s.
Radiotherapy	47 (9.0)	39 (7.4)	n.s.	n.s.
Prostatectomy + radiotherapy	21 (4.0)	13 (2.5)	n.s.	n.s.
Hormone therapy	525 (100.0)	527 (100.0)	0 (0)	0 (0)
1st generation antiandrogens	352 (67.0)	361 (68.5)	n.s.	n.s.
GnRH analogues	496 (94.5)	489 (92.8)	n.s.[h]	n.s.[h]
Bilateral orchiectomy	33 (6.3)	40 (7.6)	n.s.	n.s.
Prior docetaxel therapy, n (%)				
No	467 (89.0)	472 (89.6)	n.s.	n.s.
Yes	58 (11.0)	55 (10.4)	n.s.	n.s.
Time from start of ADT for mHSPC to randomization [months], median [Q1; Q3]	1.8 [0.9; 3.5]	1.8 [0.9; 3.5]	Not applicable[h]	Not applicable[h]
Treatment discontinuation, n (%)	177 (33.8)	284 (53.9)	n.s.[i]	n.s.
Study discontinuation, n (%)	n.s.	n.s.	n.s.	n.s.

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. [min; max].
c. IQWiG calculations from data provided in days.
d. Combination of the categories “American Indian / Alaska Native”, “other” and “multiple”, IQWiG calculation.
e. IQWiG calculation.
f. Data for WHO-PS.
g. Only patients in metastatic stage were included in the analysed subpopulation.
h. All patients started ADT at the time of study inclusion.
i. In the docetaxel arm, 29 patients never started treatment.

ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; GnRH: gonadotropin-releasing hormone; m: male; mHSPC: metastatic hormone-sensitive prostate cancer; n: number of patients in the category; N: number of randomized patients; n.s.: not specified; RCT: randomized controlled trial; SD: standard deviation; WHO-PS: World Health Organization Performance Status

The patient characteristics in the individual studies' arms are sufficiently balanced. In the studies, mean patient age was about 69 and 65 years, respectively; all patients had distant metastases, and the majority of patients exhibited a Gleason score of ≥ 8 as well as good general health (ECOG-PS or WHO-PS of 0 or 1).

The studies differed in the proportion of patients with an ECOG-PS or WHO-PS of 0, in the proportion of patients with bone metastases at study start, and in the proportion of patients with distant metastases at initial diagnosis. Differences in prior treatment cannot be fully assessed due to lack of data for the STAMPEDE study. However, differences were found in prior ADT and docetaxel treatment. These aspects are discussed in Section 2.3.3 on the similarity check.

Duration of treatment and follow-up observation

Table 10 shows the mean and median patient treatment duration as well as the mean and median follow-up observation for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT

Study **Duration of the study phase** **Outcome category**	**Apalutamide + ADT**	**Placebo + ADT**
Study with the intervention		
TITAN	**N = 525**	**N = 527**
Treatment duration [months]		
Median [Q1; Q3]	20.5 [14.9; 24.7]	18.3 [10.3; 22.9]
Mean (SD)	16.7 (8.0)	19.0 (7.8)
Follow-up observation [months]		
Overall survival		
Median [Q1; Q3]	20.4 [n.s.]	22.9 [n.s.]
Mean (SD)	n.s.	n.s.
Morbidity: skeletal-related events	No indirect comparison conducted[a]	
Health-related quality of life	No data suitable for indirect comparison available[b]	
Adverse events	n.s.	n.s.
Study with the comparator therapy	**Docetaxel + prednisolone + ADT**	**ADT**
STAMPEDE	**N = 362**	**N = 724**
Treatment duration [months]	n.s.	n.s.
Follow-up observation [months]		
Overall survival		
Median [Q1; Q3]	78.2 [n.s.]	76.4 [n.s.]
Mean (SD)	n.s.	n.s.
Morbidity: skeletal-related events	No indirect comparison conducted[a]	
Health-related quality of life	No data suitable for indirect comparison available[b]	
Adverse events	n.s.	n.s.

a. Due to insufficient similarity, no indirect comparison was conducted in the present assessment (see Section 2.4.3).
b. The TITAN and STAMPEDE studies used different instruments for measuring health-related quality of life (see Table 12).

ADT: androgen deprivation therapy; FACT-P: Functional Assessment of Cancer Therapy-Prostate; n.s.: not specified; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The treatment arms in the TITAN study exhibit no relevant differences in median and mean treatment durations or in median follow-up duration for the outcome of overall survival. For the STAMPEDE study, there is a lack of data on treatment duration. The median follow-up duration for the outcome of overall survival does not meaningfully differ between treatment arms. For both studies, data are lacking on the follow-up for AE outcomes.

Marked differences between the individual studies were found in terms of their follow-up durations. Given the employed statistical models (Cox proportional hazards models) and long

follow-up durations, the results in both studies are assumed to be of informative value. Using the observed hazard ratios and assuming proportional hazards, an adjusted indirect comparison can be conducted despite the between-study differences in follow-up durations.

2.3.3 Similarity of studies for the indirect comparison

The study characteristics described in Section 2.3.2 give rise to several aspects concerning the similarity of the studies. They are discussed in more detail below.

Similarity of study conduct

Study design

Both included studies are multicentre RCTs. While TITAN is a double-blind study, STAMPEDE is non-blinded. In subjectively recorded outcomes, lack of blinding typically leads to a high risk of bias of results. However, since no adjusted indirect comparison is conducted for any of these outcomes in the given data constellation, the lack of blinding has no effect in this regard (see Section 2.4.2).

In addition, the studies were conducted during different time periods. The STAMPEDE study already started in 2005, while the TITAN study started only in 2015.

Concomitant therapies

Due to the studies having been conducted at different times, there might be differences concerning concomitant therapies. Both studies allowed the use of pharmacological prevention and treatment of skeletal-related events. For the prevention and treatment of skeletal-related events, the TITAN study allowed drugs from the group of bisphosphonates or the drug denosumab. In the STAMPEDE study, any necessary drugs were allowed. However, the drug denosumab was approved only in 2010 and was therefore not available to included patients in the first 5 years of the STAMPEDE study period. No data are available on the concomitant therapies used in the STAMPEDE study. Therefore, it is impossible to assess the extent to which further differences in concomitant treatment exist beyond the described availability of denosumab. All in all, it is unknown how many patients received concomitant therapy for the prevention or treatment of skeletal-related events and which drugs were used for this purpose. Although the described difference does not negate the general similarity of the studies, it has been taken into account for the specific outcomes, particularly in the interpretation of results of the outcome of skeletal-related events (see Section 2.4.3).

Subsequent therapies

Given marked differences in follow-up periods and in the categorization of subsequent therapies, the data on subsequent therapies shown in Table 29 and Table 30 of the full dossier assessment for the TITAN and STAMPEDE studies are not comparable per se. However, the data show that similar therapies were generally available and used in both studies, primarily hormone therapy (e.g. abiraterone, enzalutamide) and/or chemotherapy (predominantly with docetaxel). Overall, most of the drugs used reflect the recommendations of the S3 guideline for

the early detection, diagnosis, and treatment of prostate cancer [22]. Some drugs such as enzalutamide or abiraterone were indeed available only in the later part of the STAMPEDE study. All in all, however, sufficient similarity between the two studies as a prerequisite for conducting an adjusted indirect comparison is not fundamentally questioned with regard to subsequent therapies.

Similarity of the patient population

Patient characteristics

The demographic and clinical characteristics of the included patients, such as age, ethnic/racial background, and Gleason score, are comparable in the TITAN and STAMPEDE studies.

Minor differences between the studies were found in the ECOG-PS or WHO-PS: The proportion of patients with an ECOG-PS of 0 was slightly lower in the TITAN study, at about 2/3, than in the STAMPEDE study, in which about 3/4 of patients had a WHO-PS of 0. However, since the majority of patients in both studies were in good general health (ECOG-PS/WHO-PS of 0 or 1), the study populations are deemed sufficiently similar in these aspects.

All patients included in the indirect comparison had distant metastases at study start. However, there were differences between the studies in terms of the percentage of patients with bone metastases at study start. In the TITAN study, all patients exhibited bone metastases, while in the STAMPEDE study, only 85% and 88%, respectively, did so. In addition, distant metastases were present at initial diagnosis in about 81% of patients in the TITAN study as opposed to about 95% of patients in the STAMPEDE study. In both studies, however, the majority of patients had bone metastases both at study start and at initial diagnosis. Consequently, despite the described differences, the similarity of study populations can be considered sufficient for conducting an adjusted indirect comparison.

Prior treatment

Prior ADT

Concerning prior ADT, there are differences between the TITAN and STAMPEDE studies. In the TITAN study, ADT had to have started at least 14 days and no more than 3 months before randomization. The STAMPEDE study preferentially includes patients without ADT start prior to randomization. Any existing ADT had to have been taken for no more than 12 weeks before randomization.

A TITAN inclusion criterion requires patients to have started prior ADT before randomization. In the relevant subpopulation of the STAMPEDE study, ADT for mHSPC in all patients was initiated only after randomization. Patients in the TITAN study received ADT for a median of 1.8 months before randomization. Particularly given the fact that ADT is a long-term treatment, this relatively short prior ADT compared to the total treatment duration in both studies is unlikely to have a relevant effect (see Table 10). Therefore, patients in the TITAN study are not

deemed to materially differ from the patients in the relevant STAMPEDE subpopulation at the time of randomization, for instance in terms of disease severity or risk profile.

Prior docetaxel treatment

Another between-study difference in terms of prior treatment lies in the fact that the TITAN study allowed prior docetaxel treatment (≤ 6 cycles). In the STAMPEDE study, prior chemotherapy was disallowed. However, since approx. 11% of patients in the TITAN study received prior docetaxel treatment before study inclusion, the TITAN and STAMPEDE study populations are deemed sufficiently similar in this regard.

Similarity of the common comparator

The treatment in the common comparator arm was placebo + ADT in the TITAN study and ADT in the STAMPEDE study. In both studies, ADT was allowed to be either surgical or medical, with the latter involving the administration of GnRH analogues (GnRH agonists or antagonists). Detailed data on the type of ADT used are available only for the TITAN study (see Table 9). In both studies, short-term antiandrogen administration during GnRH agonist therapy was considered appropriate. Likewise, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on prostate cancer [24] recommends the use of 1st generation antiandrogens for ≥ 7 days alongside GnRH agonists to control testosterone increases in patients with bone metastases.

The difference between the studies lies in the fact that TITAN patients had to have started ADT or GnRH agonist treatment and hence any antiandrogens before randomization. Antiandrogens had to have been discontinued before randomization. In the STAMPEDE study, ADT or GnRH agonists as well as antiandrogens, if any, were started after randomization (see above section on the similarity of prior treatment). In the TITAN common comparator arm, 68.5% of patients received prior antiandrogen therapy (see Table 9). The only information available on the use of antiandrogens in the STAMPEDE study is that, at the time of study inclusion, about 76% of the total population in both relevant study arms was to receive short-term antiandrogen therapy. Despite the fact that the study plan specified only short-term use of antiandrogens to control an increase in testosterone levels, at the time of study inclusion, long-term antiandrogen therapy was planned for about 15% of the total patient population. It is unknown how many patients in the relevant subpopulation had actually been treated with antiandrogens and for how long.

As described in the section on similarity of prior treatment, this difference in the timing of antiandrogen use relative to randomization does not fundamentally challenge the similarity of the common comparator. Nonetheless, this difference is accounted for in the interpretation of the results on patient-relevant outcomes (see Section 2.4.3).

Summary

All things considered, the TITAN and STAMPEDE studies are deemed sufficiently similar for conducting an adjusted indirect comparison via the common comparator of placebo + ADT or

ADT. The treatment-related uncertainty in the common comparator arm is accounted for in the interpretation of results.

This view concurs with the company's insofar as the company considers the TITAN and STAMPEDE studies sufficiently similar for conducting an adjusted indirect comparison. In deviation, the company deems the GETUG and CHAARTED studies relevant for the assessment as well (see Section 2.3).

2.3.4 Risk of bias across outcomes (study level)

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

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

Study	Adequate generation of the randomization sequence	Allocation concealment	Blinding		Absence of reporting bias	No other aspects	Risk of bias at study level
			Patients	Providers			
Study with the intervention							
TITAN	Yes	Yes	Yes	Yes	Yes	Yes	Low
Study with the comparator therapy							
STAMPEDE	Yes	Yes	No	No	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both included studies. This concurs with the company's assessment. The open-label design of the STAMPEDE study is commented in Section 2.4 under risk of bias at outcome level.

2.4 Results on added benefit

2.4.1 Included outcomes

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

- Mortality
  - Overall survival
- Morbidity
  - Skeletal-related events

- Health-related quality of life
- Adverse events
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Further specific AEs, if any

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

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

Table 12: Matrix of outcomes – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT

Study	Outcomes					
	Overall survival	Skeletal-related events	Health-related quality of life	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs
Study with the intervention						
TITAN	Yes	Yes[a]	No[b]	Yes	Yes[a]	Yes
Studies with the comparator therapy						
STAMPEDE	Yes	Yes[a]	No[b]	Yes	Yes[a]	No[c]

a. The present assessment foregoes an indirect comparison for the outcome due to insufficient similarity (see Section 2.4.3).
b. The studies used different instruments for measuring health-related quality of life (TITAN used FACT-P, while STAMPEDE used EORTC QLQ-C30). Therefore, no indirect comparison is possible.
c. No data available on the outcome.

AE: adverse event; ADT: androgen deprivation therapy; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire – Cancer 30; FACT-P: Functional Assessment of Cancer Therapy-Prostate; RCT: randomized controlled trial; SAE: serious adverse event

No specific AEs were selected since the certainty of results for AE outcomes was too low for conducting an adjusted indirect comparison (see Section 2.4.3).

Relevance of the presented surrogate validation study

In its assessment of added benefit for the outcome of overall survival, the company included the results of a study it conducted to validate the outcome of rPFS as a surrogate for overall survival in the therapeutic indication of metastatic prostate cancer. The company does not provide a rationale for the need to use rPFS as a surrogate for overall survival.

Using a correlation-based method, the company aimed to validate the outcome of rPFS as a surrogate for overall survival. It intended to derive a conclusion on the effect of treatment on overall survival by means of calculating a surrogate threshold effect (STE) from the effect estimation for rPFS. This method is generally suitable for surrogate validation. When defining the method, the company referred to the recommendations of Rapid Report A10-05 [25] and the publication Schürmann 2016 [26].

The company's study pool for surrogate validation comprises a total of 16 RCTs [13,27-41]. For this study pool, the resulting STE is 0.67. The company then excluded 1 RCT [27] and recalculated the STE. To justify the exclusion of the above RCT, the company discussed deviations in the operationalization of rPFS, potentially leading to higher data heterogeneity. For the smaller study pool, the resulting STE is 0.80. This STE was then used by the company in its further procedure. The 95% confidence interval (CI) for rPFS from the indirect comparison used by the company for deriving the added benefit (TITAN versus GETUG, CHAARTED) is [0.57; 0.96]. The company also calculated the 95% CIs for the study pool included in this benefit assessment (TITAN versus STAMPEDE). This 95% CI is [0.53; 0.91]. For both indirect comparisons, the respective 95% CI is therefore not fully below the STE thresholds calculated by the company. No different results were found for the third calculation presented by the company, TITAN versus GETUG, CHAARTED, STAMPEDE (95% CI: [0.57; 0.91]). The results of the available validation study therefore fail to show rPFS to be a valid surrogate for the outcome of overall survival. Consequently, in deviation from the company's approach, the outcome of rPFS is not used as a valid surrogate for overall survival in the present benefit assessment. Therefore, the company's surrogate validation is not further commented.

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 the study and outcome levels – RCT, indirect comparison: apalutamide + ADT versus docetaxel + ADT + prednisolone

Study	Study level	Outcomes					
		Overall survival	Skeletal-related events	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
Study with the intervention							
TITAN	L	L	L	–[a]	H[b]	L	H[b]
Study with the comparator therapy							
STAMPEDE	L	L	L	–[a]	L[c]	–[d]	L[c]

a. The studies used different instruments for measuring health-related quality of life; therefore, no indirect comparison is possible.
b. The percentage of patients with incomplete follow-up due to treatment discontinuation may be high and differ between treatment arms (apalutamide + ADT: 34%; placebo + ADT: 54%).
c. Potential low bias of effect estimations for the period in which patients in the intervention arm (docetaxel + prednisolone + ADT) were followed up for the outcome (approximately 6–7 months).
d. No data available on the outcome.

AE: adverse event; ADT: androgen deprivation therapy; CTCAE: Common Terminology Criteria for Adverse Events; h: high; MedDRA: Medical Dictionary for Regulatory Activities; L: low; RCT: randomized controlled trial; SAE: serious adverse event

TITAN study

For the TITAN study, a low risk of bias was identified for the results on overall survival, skeletal-related events, and discontinuation due to AEs. A high risk of bias was found for the results on the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3), which were each followed for up to 30 days after treatment discontinuation due to potentially high percentages of patients with incomplete follow-up and potential differences in these percentages between treatment arms (patients with treatment discontinuation over the course of the study: apalutamide + ADT: 34%; placebo + ADT: 54%). While the company likewise rates the risk of bias as high for the results on SAEs and severe AEs (CTCAE grade ≥ 3), it does so due to possible informative censoring resulting from different follow-up durations.

STAMPEDE study

For the STAMPEDE study, a low risk of bias was found for the results on overall survival, skeletal-related events, SAEs, and severe AEs (CTCAE grade ≥ 3). Regarding the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3), the follow-up duration differed markedly between treatment arms. This was due to the following reasons: Patients in the ADT arm were followed for up to 30 days after the end of ADT, which was continued for at least 2 years or until

progression or treatment discontinuation for other reasons. Patients in the docetaxel + prednisolone + ADT arm were followed for up to 30 days after the end of docetaxel treatment. Docetaxel treatment, however, was limited to a maximum of 6 cycles in accordance with approval; ADT was continued beyond that time. The follow-up of the patients in the docetaxel + prednisolone + ADT arm was based on the duration of docetaxel treatment; consequently, patients in the docetaxel + prednisolone + ADT arm were followed concerning AEs for a much shorter time overall, at most for 6 to 7 months from randomization (see Appendix A of the full dossier assessment). The effect estimation presented by the company, a hazard ratio from a Cox proportional hazards model, is appropriate in the given data constellation and is used. However, the effect estimation is interpretable only for this time period of about 6 to 7 months and potentially associated with minor bias.

2.4.3 Results

Table 14 and Table 15 summarize the results for the comparison of apalutamide + ADT with docetaxel + prednisolone + ADT in patients with mHSPC who are in good general health. Where necessary, the data from the company's dossier are supplemented by IQWiG calculations. Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, AEs, time to event) – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Outcome category **Outcome** **Comparison** **Study**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**(Placebo) + ADT** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT** **HR [95% CI]; p-value**
Mortality					
All-cause mortality					
Study with apalutamide + ADT					
TITAN	525	NR 83 (15.8)	527	NR 117 (22.2)	0.67 [0.51; 0.89]; 0.005[a]
Study with docetaxel + prednisolone + ADT					
STAMPEDE	362	59.1 [n.s.] 225 (62.2)	724	43.1 [n.s.] 494 (68.2)	0.81 [0.69; 0.95]; 0.003[b]
Indirect comparison: **apalutamide + ADT vs. docetaxel + prednisolone + ADT[c]**					0.83 [0.60; 1.14]; 0.247
Morbidity					
Time to 1st skeletal-related event					
Study with apalutamide + ADT					
TITAN[d]	525	NR 53 (10.1)	527	NR 64 (12.1)	0.80 [0.56; 1.15]; 0.225[a]
Study with docetaxel + prednisolone + ADT					
STAMPEDE[e]	362	95.80 [n.s.] 132 (36.5)	724	49.68 [n.s.] 357 (49.3)	0.63 [0.51; 0.76]; n.s.
Indirect comparison: **apalutamide + ADT versus docetaxel + prednisolone + ADT**					–[f]
Adverse events[g]					
AEs (supplementary information)					
Study with apalutamide + ADT					
TITAN	524	0.95 [0.95; 1.25] 507 (96.8)	527	1.71 [1.38; 1.87] 509 (96.6)	–
Study with docetaxel + prednisolone + ADT					
STAMPEDE	335	0.82 [n.s.] 327 (97.6)	724	1.48 [n.s.] 693 (95.7)	–

Table 14: Results (mortality, morbidity, AEs, time to event) – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Outcome category **Outcome** **Comparison** **Study**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**(Placebo) + ADT** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT** **HR [95% CI]; p-value**
SAEs					
Study with apalutamide + ADT					
TITAN	524	NR 104 (19.8)	527	NR 107 (20.3)	0.91 [0.70; 1.20]; 0.516[a]
Study with docetaxel + prednisolone + ADT					
STAMPEDE	335	NR 96 (28.7)	724	NR 80 (11.0)	9.04 [5.92; 13.79]; n.s.
Indirect comparison:					
apalutamide + ADT vs. docetaxel + prednisolone + ADT[c]					0.10 [0.06; 0.17]; < 0.001
Severe AEs (CTCAE grade ≥ 3)					
Study with apalutamide + ADT					
TITAN	524	NR [23.5; NR] 223 (42.6)	527	NR [20.3; NR] 222 (42.1)	0.99 [0.83; 1.20]; 0.961[a]
Study with docetaxel + prednisolone + ADT					
STAMPEDE	335	NR 108 (32.2)	724	NR 219 (30.2)	2.39 [1.84; 3.11]; n.s.
Indirect comparison:					
apalutamide + ADT versus docetaxel + prednisolone + ADT					–[h]
Discontinuation due to AEs					
Study with apalutamide + ADT					
TITAN	524	NR 42 (8.0)	527	NR 28 (5.3)	1.41 [0.87; 2.27]; 0.162
Study with docetaxel + prednisolone + ADT					
STAMPEDE				n.s.	
Indirect comparison:					
apalutamide + ADT versus docetaxel + prednisolone + ADT					–[i]

Table 14: Results (mortality, morbidity, AEs, time to event) – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT (multi-page table)

Outcome category **Outcome** **Comparison** **Study**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT**		**(Placebo) + ADT**		**Apalutamide + ADT vs. docetaxel + prednisolone + 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. Hazard ratio (including 95% CI) calculated using stratified Cox proportional hazards model, p-value using stratified log rank test; stratification variables: Gleason score at diagnosis (≤ 7 months vs. > 7 months), geographic region (North America / EU vs. other countries) and prior docetaxel treatment (yes vs. no). b. Hazard ratio (including 95% CI) calculated using adjusted and stratified Cox proportional hazards model, p-value using stratified log rank test; adjustment variables: lymph node status (N0 vs. N+ vs. Nx), age (< 70 years vs. ≥ 70 years), ECOG Performance Score (0 vs. 1), use of aspirin/NSAIDs, planned use of radiotherapy; stratification variables: time period regarding change in multi-arm design and change in standard treatment (ADT). c. Adjusted indirect comparison according to Bucher [42]). d. Defined as the occurrence of a symptomatic pathological fracture, spinal cord compression, radiotherapy for bone metastases, or surgical procedure at the bone. e. Defined as the occurrence of pathological fractures, spinal cord compression, or the need for palliative radiotherapy for bone metastases (for pain relief or fracture prevention) or a surgical procedure on the bone (preventatively or for fracture treatment). f. The present assessment does not include an indirect comparison regarding this outcome due to insufficient similarity (see Section 2.4.3). g. For both studies, AE data include events which are also attributable to symptoms, such as spinal cord compression or urinary retention. However, they occurred in few patients and therefore have little effect on the total rates of AE outcomes (see Appendix B of the full dossier assessment). h. In the absence of the certainty of results required for conducting an adjusted indirect comparison, no indirect comparison has been calculated (see Section 2.4.3). i. No data available on the outcome from the STAMPEDE study. ADT: androgen deprivation therapy; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; n.s.: not specified; RCT: randomized controlled trial					

Table 15: Results (health-related quality of life) – RCT, indirect comparison: apalutamide + ADT versus docetaxel + prednisolone + ADT

Outcome category **Outcome**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT**			**(Placebo) + ADT**			**Apalutamide + ADT vs. docetaxel + prednisolone + ADT**
Comparison **Study**	**L[a]**	**Values at study start Mean (SD)**	**Change after 12 months Mean (SE)**	**L[a]**	**Values at study start Mean (SD)**	**Change after 12 months Mean (SE)**	**MD [95% CI]; p value** **Hedges' g [95% CI]**
Health-related quality of life							
FACT-P (total score)[b]							
Study with apalutamide + ADT							
TITAN	n.s.	112.8 (20.2)	n.s.	n.s.	111.5 (19.4)	n.s.	0.90 [−1.43; 3.23]; 0.449[c] −0.05 [−0.21; 0.12]
Study with docetaxel + prednisolone + ADT							
STAMPEDE	No data suitable for indirect comparison available[d]						
Indirect comparison: **apalutamide + ADT versus docetaxel + prednisolone + ADT**							–[d]

a. Number of patients considered in the analysis for calculating the effect estimation; the figures at study start (and at other times, if any) may be based on other patient numbers.
b. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for apalutamide + ADT.
c. 95% CI and p-value: IQWiG calculation assuming asymptotic normal distribution.
d. In the STAMPEDE study, health-related quality of life was measured using EORTC QLQ-C30. Therefore, it is not possible to conduct an indirect comparison.

ADT: androgen deprivation therapy; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of randomized patients; n.s.: not specified; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

One RCT was included on each side of the present adjusted indirect comparison. Hence, the check for homogeneity was omitted. Since no directly comparative study is available for the comparison of apalutamide + ADT versus docetaxel + prednisone/prednisolone + ADT, it is impossible to check the consistency of results. Hence, the adjusted indirect comparisons have, at best, low certainty of results. On the basis of the available data from the adjusted indirect comparison, at most hints, e.g. of an added benefit, can therefore be derived.

This concurs with the company's view insofar as the company derives at most a hint for each of the included outcomes. In deviation from the company's approach, this assessment includes only the STAMPEDE study on the comparator side of the adjusted indirect comparison. The

company presented an adjusted indirect comparison for the TITAN versus STAMPEDE studies as well as for TITAN versus STAMPEDE, CHAARTED and GETUG (see Section 2.3). To derive the added benefit, the company used, to the extent possible, the results of the adjusted comparison between TITAN and the 3 named studies on the comparator side.

Mortality

Overall survival

For the outcome of overall survival, the adjusted indirect comparison shows no statistically significant difference between apalutamide + ADT versus docetaxel + prednisolone + ADT. The aspects described regarding the similarity check (Section 2.3.3) are not deemed to materially impact this result. Consequently, there is no hint of added benefit of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; an added benefit is therefore not proven.

In addition to presenting results on the outcome of overall survival, the company's dossier contains data for validating rPFS as a surrogate for the outcome of overall survival. From the combined analysis of the results for the outcomes of overall survival and rPFS, the company derives a hint of added benefit for the outcome category of mortality. However, the validation data are unsuitable for demonstrating the validity of rPFS as a surrogate for overall survival in the present therapeutic indication. In the benefit assessment, rPFS is therefore not deemed a valid surrogate for overall survival (see Section 2.4.1).

Morbidity

Skeletal-related events

The common comparator arms of the TITAN and STAMPEDE studies exhibit markedly different rates of patients with an event; this negates the similarity of the two studies for the outcome. For the 24-month time point, for example, a skeletal-related event is found in about 15% of patients in the TITAN common comparator arm and in about 38% in that of the STAMPEDE study (see full dossier assessment, Figures 4 and 5, Appendix A: rates estimated on the basis of the available Kaplan-Meier curves). While both studies generally allowed drug-based prophylaxis of skeletal-related events, no data are available as to how many patients actually received concomitant treatment for skeletal-related events and which drugs were used (also see Section 2.3.3).

Consequently, no data usable for an adjusted indirect comparison are available for the outcome of skeletal-related events. This does not result in a hint of added benefit; an added benefit is therefore not proven.

This deviates from the approach of the company, which conducted an adjusted indirect comparison for the outcome of skeletal-related events, but did not derive any added benefit from it.

Health-related quality of life

The TITAN and STAMPEDE studies used different instruments for measuring the outcome of health-related quality of life; hence, no usable data for an indirect comparison are available (see Section 2.4.1). Consequently, there is no hint of added benefit of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; an added benefit is therefore not proven. This concurs with the company's assessment.

Adverse events

SAEs

On the apalutamide + ADT side of the adjusted indirect comparison, the only available result for the outcome of SAEs is from one study (TITAN) with a high risk of bias at the outcome level. At first sight, the prerequisites are therefore not met for deriving any conclusions of adequate certainty of results on added benefit from an adjusted indirect comparison. For this outcome, however, both the STAMPEDE study and the adjusted indirect comparison via the common comparator of placebo + ADT or ADT show a large effect estimation. Given the present data constellation, the advantage in the adjusted indirect comparison cannot be assumed to be fully negated by potential bias (Section 2.4.2). Hence, despite the high risk of bias at outcome level in the TITAN study, the qualitative certainty of results is sufficiently high to allow interpretation of the present effect. Furthermore, the above-described aspects of study similarity (Section 2.3.3) do not preclude the conduct of an adjusted indirect comparison. Consequently, in the present situation, it is possible to derive a hint of greater or lesser harm of apalutamide + ADT.

The adjusted indirect comparison for the outcome of SAE shows a marked statistically significant difference in favour or apalutamide + ADT in comparison with docetaxel + prednisone + ADT. Given the data constellation in the STAMPEDE study, this conclusion applies to the time period of 6 to 7 months (see Section 2.4.2). This results in a hint of lesser harm of apalutamide + ADT. However, the effect size cannot be quantified due to the present data constellation. This deviates from the assessment of the company, which derived a hint of considerable added benefit on the basis of the outcomes of SAEs and severe AEs.

Severe AEs (CTCAE grade ≥ 3)

For the results on the outcome of severe AEs (CTCAE grade ≥ 3), there is a high risk of bias in the TITAN study (see Section 2.4.2). Hence, any effect estimation for the indirect comparison regarding this outcome is not sufficiently reliable.

For the outcome of severe AEs (CTCAE grade ≥ 3), there was therefore no hint of greater or lesser harm of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; therefore, there is no proof of greater or lesser harm.

This deviates from the company's assessment, which used the outcome of severe AEs (CTCAE grade ≥ 3) in conjunction with the outcome of SAEs to derive a hint of considerable added benefit.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, data are available exclusively for the intervention side of the indirect comparison (see Section 2.4.1). Consequently, there is no hint of greater or lesser harm of apalutamide + ADT in comparison with docetaxel + prednisolone + ADT; greater or lesser harm is therefore not proven.

This concurs with the approach of the company, which likewise did not use the outcome of discontinuation due to AEs in its assessment.

2.4.4 Subgroups and other effect modifiers

The present assessment accounts for the following potential effect modifier:

- age (< 65 / ≥ 65 to 74 / ≥ 75).

In the TITAN and STAMPEDE studies, the above attribute was defined a priori as a potential effect modifier.

The attribute of sex was disregarded in the present benefit assessment since mHSPC affects exclusively males.

Interaction tests are conducted if at least 10 patients per subgroup are included in the analysis. For binary data, another requirement is that at least 1 subgroup must exhibit 10 events.

Results are reported only if an effect modification is found with a statistically significant interaction between treatment and subgroup attribute (p-value < 0.05). In addition, subgroup results are presented only if a statistically significant and relevant effect was found in at least one subgroup.

For the present benefit assessment, no relevant effect modification was found for the included outcomes on the basis of the methods described above.

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 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 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).

Table 16: Extent of added benefit at outcome level: apalutamide + ADT versus docetaxel + prednisolone + ADT

Outcome category **Outcome**	**Apalutamide + ADT vs. docetaxel + prednisolone + ADT** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median time to event: NR vs. 59.1 HR: 0.83 [0.60; 1.14] p = 0.247	Lesser/added benefit not proven
Morbidity		
Skeletal-related events	Indirect comparison not conducted[c]	Lesser/added benefit not proven
Health-related quality of life		
FACT-P	No data suitable for indirect comparison available[d]	Lesser/added benefit not proven
Adverse events		
SAEs	Median: NR vs. NR HR: 0.10 [0.06; 0.17] p < 0.001 Probability: hint	Outcome category: serious/severe adverse events $CI_u < 0.75$ Lesser harm; extent: non-quantifiable
Severe AEs (CTCAE grade ≥ 3)	No usable data[e]	Greater/lesser harm not proven
Discontinuation due to AEs	Insufficient data available[f]	Greater/lesser harm not proven

a. Probability given if statistically significant differences are present.
b. Depending on outcome category, effect size estimates use different limits based on the upper confidence limit (CI_u).
c. No indirect comparison was conducted due to insufficient similarity (see Section 2.4.1).
d. The studies used different instruments for measuring health-related quality of life (TITAN used FACT-P, while STAMPEDE used EORTC QLQ-C30). Therefore, no indirect comparison is possible.
e. Due to insufficient certainty of results in the TITAN study, no indirect comparison was calculated (see Section 2.4.1).
f. The STAMPEDE study did not provide any data on this outcome.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: Hazard Ratio; SAE: serious adverse event;

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
Serious/severe AEs ▪ SAEs: Hint of lesser harm – extent: non-quantifiable	–
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

All things considered, the results show an exclusively positive effect for apalutamide + ADT in the category of adverse events. The marked effect on the outcome of SAEs is not called into question by any disadvantages.

In summary, for patients with mHSPC who are in good general health, there is a hint of non-quantifiable added benefit of apalutamide in comparison with the ACT.

The assessment described above deviates from that of the company, which derived a hint of considerable added benefit for the entire therapeutic indication of mHSPC.

Table 18 presents a summary of the results of the benefit assessment of apalutamide in comparison with the ACT.

Table 18: Apalutamide – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
In adult men for the treatment of mHSPC in combination with ADT	▪ Only for patients with distant metastases (stage M1) who are in good general health (ECOG-PS/WHO-PS 0 to 1 or Karnofsky index ≥ 70%): conventional ADT in combination with docetaxel and prednisone or prednisolone or[d] ▪ Only for patients with newly diagnosed high-risk metastatic hormone-sensitive prostate cancer: conventional ADT in combination with abiraterone acetate and prednisone or prednisolone	Hint of non-quantifiable added benefit [b, c]

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the TITAN study. The STAMPEDE study allowed the inclusion of patients with a WHO-PS of 2. However, the majority of patients had a WHO-PS of 0. No specific data are available on the number of patients with a WHO-PS of 2 (see Table 9). The conclusion on added benefit therefore applies to patients in good general health (as measured by ECOG/WHO 0–1).
c. Patients with brain metastases were excluded from the TITAN and STAMPEDE studies. It remains unclear whether the observed effects translate to patients with brain metastases.
d. The listed therapies are ACTs for the respective listed subpopulation. The subpopulations overlap. Only for this overlapping set of patients do docetaxel + prednisolone or prednisone + ADT as well abiraterone acetate + prednisolone or prednisone + ADT represent ACTs ("OR-operation").

ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; mHSPC: metastatic hormone-sensitive prostate cancer; WHO-PS: World Health Organization Performance Status

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

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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