IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Abiraterone acetate (prostate cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Abirateronacetat (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 March 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

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

Medical and scientific advice:

- Gerhard Jakse, Faculty of Medicine, Rhine-Westphalian Technical University (RWTH) Aachen, Germany

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

IQWiG employees involved in the dossier assessment:

- Anke Penno
- Christiane Balg
- Catharina Brockhaus
- Michaela Florina Kerekes
- Regine Potthast
- Min Ripoll
- Volker Vervölgyi
- Siw Waffenschmidt

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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Levels
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCP	good clinical practice
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LH-RH	luteinizing hormone-releasing hormone
mHSPC	metastatic hormone sensitive prostate cancer
P	prednisone/prednisolone
PCS	prostate cancer subscale of the FACT-P
PRS	pain-related subscale of the FACT-P
PWB	physical well-being subscale of the FACT-P
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TOI	Trial Outcome Index
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 abiraterone acetate (hereinafter referred to as "abiraterone"). 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 15 December 2017.

Research question

The aim of the present report was the assessment of the added benefit of abiraterone in combination with prednisone/prednisolone (P) and androgen deprivation therapy (ADT) (hereinafter referred to as "abiraterone-P-ADT") in comparison with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC).

Table 2: Research questions of the benefit assessment of abiraterone

Research question	Therapeutic indication	ACT[a]
1	Patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC)	▪ conventional androgen deprivation therapy (ADT)[b] ▪ if applicable, in combination with a non-steroidal anti-androgen (flutamide or bicalutamide)

a: Presentation of the respective ACT specified by the G-BA.
b: Surgical castration or medical castration using treatment with LH-RH analogues or GnRH antagonists.
ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; LH-RH: luteinizing hormone-releasing hormone; mHSPC: metastatic hormone sensitive prostate cancer

The company concurred with the G-BA's specification on the ACT.

The assessment of the added benefit was conducted in comparison with the ACT and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool and study characteristics

The 2 studies LATITUDE and STAMPEDE were included in the present benefit assessment.

The LATITUDE study, conducted by the company, was the basis for the extension of approval of abiraterone in newly diagnosed high risk mHSPC. The STAMPEDE study was a third-party study, which, according to the information provided in the available documents, is financially

supported by the company, and in which the company is involved as an advisor with regard to content.

LATITUDE

The LATITUDE study was a randomized, double-blind, placebo-controlled parallel-group study on the comparison of treatment with abiraterone in combination with prednisone and ADT (abiraterone-P-ADT) versus treatment with ADT plus additional administration of placebo.

The study included adult patients with newly diagnosed (within 3 months before randomization) high risk mHSPC. Presence of high risk mHSPC was defined by the presence of at least 2 of the 3 following high risk criteria: 1) Gleason score ≥ 8 in the primary tumour, 2) presence of ≥ 3 bone metastases, and 3) presence of visceral metastasis (excluding lymph node metastasis). The metastatic stage had to be documented by the presence of distant metastasis (M1). The following patients were not included in the study: patients with brain metastasis, metastatic recurrence, impaired cardiac, haematological, hepatic or renal function, adrenal disorders, uncontrolled hypertension or an Eastern Cooperative Oncology Group (ECOG) Performance Status of > 2. The maximum allowed pretreatment of the patients before the start of the study was one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 28 days prior to the start of treatment. In addition, patients were allowed prior ADT within 3 months before the start of the study.

A total of 1209 patients were included in the study until December 2014. Randomization was stratified by presence of visceral metastasis (yes/no) and ECOG Performance Status (0 or 1 versus 2). Data of 597 patients in the abiraterone arm and of 602 patients in the comparator arm were included in the analysis of the study.

The patients received either abiraterone (1000 mg daily) in combination with prednisone (5 mg daily) and ADT or ADT and abiraterone and prednisone as placebo administration. The choice of the adequate ADT for the patient (surgical or medical with luteinizing hormone-releasing hormone [LH-RH] agonists) was at the treating physician's discretion. Treatment was to be conducted until disease progression, occurrence of unacceptable toxicity, withdrawal of consent or decision by the treating physician. Follow-up observation of the patients after progression or discontinuation of treatment with abiraterone was up to 60 months in total or until the end of the study for the analysis of overall survival.

The LATITUDE study was initiated on 25 January 2013 and was stopped prematurely following a positive result of a planned interim analysis for the outcomes "overall survival" and "progression-free survival" (data cut-off on 31 October 2016).

STAMPEDE

The STAMPEDE study is a randomized, open-label, multi-arm and multi-phase platform trial in advanced or metastatic prostate cancer on the comparison of different systemic drug therapies.

The STAMPEDE study includes patients with prostate cancer for whom long-term ADT is intended and whose disease concurs with one of the following 3 groups: 1) newly diagnosed disease with presence of distant metastasis or lymph node metastasis, 2) newly diagnosed disease with high risk locally advanced prostate cancer without distant metastasis or lymph node metastasis, 3) recurrent locally advanced or metastatic disease after prior radiotherapy and/or surgery. Only the patients in group 1 with distant metastasis were relevant for the present benefit assessment (see below). Patients from group 1 and 2 were allowed to have received ADT within 3 months before start of the study. Patients with brain metastasis, cardiovascular or cerebrovascular disease, impaired haematological, hepatic or renal function, or a World Health Organization (WHO) Performance Status of > 2 are not included in the study.

The STAMPEDE study comprises a total of 11 study arms (arms A to L). Only the comparison between study arm G (abiraterone-P-ADT) and study arm A (ADT, hereinafter referred to as "comparator arm") was relevant for the present benefit assessment. A total of 960 patients were allocated to the abiraterone-P-ADT arm, and 957 patients to the comparator arm (ADT). Treatment and observation of the patients in these study arms are ongoing. The patients receive either abiraterone (1000 mg daily) in combination with prednisone (5 mg daily) and ADT or ADT. ADT in the STAMPEDE study can be surgical or medical with LH-RH agonists or antagonists; the choice of ADT is at the treating physician's discretion. Treatment of the patients is until disease progression, unacceptable toxicity, or decision by the physician; follow-up observation after progression or discontinuation of treatment is unlimited or until withdrawal of consent.

Only a subpopulation of the patients included for the comparison of abiraterone-P-ADT with ADT was relevant. The company therefore presented the results of the patients with distant metastasis (hereinafter referred to as "M1 patient population") in the dossier. This patient population comprised 500 patients in the abiraterone-P-ADT arm and 502 patients in the ADT arm. About 6% of the patients in this subpopulation did not fulfil the criterion of newly diagnosed prostate cancer. Since no universally accepted definition was available, the criteria of the LATITUDE study were used to check whether these were patients with high risk mHSPC. The proportion of patients who concur with the high risk definition of the approval study LATITUDE could not be inferred from the published patient characteristics of the M1 patient population of the STAMPEDE study.

Inclusion of the studies in the derivation of the added benefit

Despite the described uncertainties, the M1 patient population of the STAMPEDE study was overall a sufficient representation of the target population and was included in the present benefit assessment in addition to the LATITUDE study. In the comparison of both studies, the

patients of the LATITUDE study concurred more closely with the target population of the present benefit assessment than the M1 patient population of the STAMPEDE study, however.

In principle, the results of the LATITUDE study and of the STAMPEDE study were considered jointly. In case of decisive heterogeneity of the results, the LATITUDE study was used primarily for conclusions on benefit because the patient population of the LATITUDE study was more similar to the target population.

Risk of bias

The risk of bias at study level for the LATITUDE study was rated as low. For the STAMPEDE study, reporting was incomplete, however. Without further explanation, all planned analyses on the outcomes "European Quality of Life-5 Dimensions 5 Levels (EQ-5D-5L)" and "European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and Prostate 25 (EORTC QLQ-C30 and PR25)" were missing. It is unclear whether this non-reporting of the results was event-driven. The risk of bias at study level was rated as low. The present assessment considered the incomplete reporting for specific outcomes and in the derivation of the added benefit.

The risk of bias for the outcome "overall survival" (LATITUDE and STAMPEDE) at outcome level was rated as low.

Due to the different median treatment durations driven by disease progression and the resulting very different observation periods, the risk of bias for all further outcomes of the categories of morbidity, health-related quality of life and side effects, except discontinuation due to adverse events (AEs), was rated as high for the LATITUDE study. The risk of bias was rated as low for the outcome "symptomatic skeletal-related events" for the STAMPEDE study. For further outcomes (except overall survival), no results relevant for the present benefit assessment were presented for the study.

Based on the available data, at most proof, e.g. of an added benefit, can be derived for the outcome "overall survival" and "skeletal-related events", at most an indication for the outcome "discontinuation due to AEs", and at most a hint for all other outcomes.

Results

Overall survival

The meta-analysis showed a statistically significant difference in favour of abiraterone-P-ADT versus ADT between the treatment groups for the outcome "overall survival". This resulted in proof of an added benefit of abiraterone-P-ADT in comparison with ADT for this outcome.

Morbidity – skeletal-related events

The meta-analysis showed considerable unexplained heterogeneity between the studies for the outcome "skeletal-related events" so that no pooled effect estimate was calculated. A statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT was

shown in both studies. Due to the uncertainty to what extent the STAMPEDE study represents the target population, the LATITUDE study was primarily considered. Due to the high risk of bias for this outcome in the LATITUDE study, only a hint could be derived initially. Since the effect estimations of both studies pointed in the same direction and were rated to have a low risk of bias for the STAMPEDE study, the certainty of conclusions was upgraded to an indication.

Morbidity – symptoms (EORTC QLQ-C30 and PR25)

The STAMPEDE study recorded the outcome "symptoms" with the questionnaires EORTC QLQ-C30 and PR25, but results were reported neither for the total population nor for the M1 patient population of the study. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

Morbidity – health status (EQ-5D VAS)

A statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT was shown for the LATITUDE study. The extent of this effect in this non-serious/non-severe outcome was no more than marginal, however.

The STAMPEDE study recorded the outcome "health status" with the EQ-5D visual analogue scale (VAS), but results were reported neither for the total population nor for the M1 patient population of the study.

Overall, there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

Morbidity – pain

The LATITUDE study showed a statistically significant difference in favour of abiraterone-P-ADT in comparison with ADT for the outcome "pain", analysed using worst pain (Brief Pain Inventory-Short Form [BPI-SF] Item 3). This resulted in a hint of an added benefit of abiraterone-P-ADT in comparison with ADT for worst pain (BPI-SF Item 3).

The STAMPEDE study recorded the outcome "pain" with the EORTC QLQ-C30 pain symptom scale, but results were reported neither for the total population nor for the M1 patient population of the study.

Morbidity – pain interference

The LATITUDE study showed a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT for pain interference (BPI-SF Items 9 a–g). However, the 95% confidence interval (CI) of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant.

This resulted in no hint of an added benefit of abiraterone-P-ADT in comparison with ADT for the outcome "pain interference" (BPI-SF Items 9 a–g); an added benefit is therefore not proven.

Morbidity – fatigue

The LATITUDE study showed a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT for the outcome "fatigue", analysed using worst fatigue (Brief Fatigue Inventory [BFI] Item 3). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT for worst fatigue; an added benefit is therefore not proven.

The STAMPEDE study recorded the outcome "fatigue" with the EORTC QLQ-C30 fatigue symptom scale, but results were reported neither for the total population nor for the M1 patient population of the study.

Morbidity – fatigue interference

The LATITUDE study showed a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT for the outcome "fatigue interference" (BFI Items 4 a–f). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the clinical irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant.

Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT for the outcome "fatigue interference"; an added benefit is therefore not proven.

Health-related quality of life (FACT-P)

For the outcome "health-related quality of life", measured in the LATITUDE study with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT was shown in the FACT-P total score. This resulted in a hint of an added benefit of abiraterone-P-ADT in comparison with ADT.

Health-related quality of life (EORTC QLQ-C30)

The STAMPEDE study recorded the outcome "health-related quality of life" with the EORTC QLQ-C30 questionnaire, but results were reported neither for the total population nor for the M1 patient population of the study. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

Side effects – severe adverse events (Common Terminology Criteria for Adverse events [CTCAE] grade 3–4)

Results for the outcome "severe AEs" were only available for the LATITUDE study. The LATITUDE study showed a statistically significant difference to the disadvantage of abiraterone-P-ADT in comparison with ADT. This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

Side effects – cardiac failure

There were no usable data as event time analyses for the outcome "cardiac failure" recorded for the LATITUDE study.

Side effects – ischaemic heart disease

There were no usable data as event time analyses for the outcome "ischaemic heart disease" recorded for the LATITUDE study.

Side effects – hypokalaemia (CTCAE grade 3–4)

Results for the outcome "hypokalaemia" (CTCAE grade 3–4) were only available for the LATITUDE study. The LATITUDE study showed a statistically significant effect to the disadvantage of abiraterone-P-ADT in comparison with ADT. This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

Side effects – alanine aminotransferase increased (CTCAE grade 3–4)

Results for the outcome "alanine aminotransferase increased" (CTCAE grade 3–4) were only available for the LATITUDE study. The LATITUDE study showed a statistically significant effect to the disadvantage of abiraterone-P-ADT in comparison with ADT. This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

Side effects – aspartate aminotransferase increased (CTCAE grade 3–4)

Results for the outcome "aspartate aminotransferase increased" (CTCAE grade 3–4) were only available for the LATITUDE study. A statistically significant effect to the disadvantage of abiraterone-P-ADT in comparison with ADT was shown. This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

Further outcomes

No statistically significant differences between the groups were shown for the following outcomes: symptomatic local progression, serious AEs (SAEs), discontinuations due to AEs, and fluid retention/oedema. This resulted in no hint of an added benefit or lesser or greater harm of abiraterone-P-ADT in comparison with ADT for these outcomes.

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

In the overall consideration, there is proof, an indication and hints of positive effects of abiraterone in the outcome categories of mortality, morbidity and health-related quality of life, as well as hints of negative effects in the outcome category of side effects.

The positive effects with the extents "minor", "considerable" and "major" are accompanied by negative effects with the same extent. There were no usable results for 2 outcomes regarding harm.

For the STAMPEDE study, there were no results for several outcomes that were recorded, but not reported. It cannot be assumed, however, that these would have a decisive negative influence on the overall result of the present benefit assessment.

Overall, there is proof of considerable added benefit of abiraterone-P-ADT in comparison with ADT in patients with newly diagnosed high risk mHSPC.

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

Table 3: Abiraterone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC)	▪ conventional androgen deprivation therapy (ADT)[b] ▪ if applicable, in combination with non-steroidal anti-androgens (flutamide or bicalutamide)	Proof of considerable added benefit[c]
a: Presentation of the respective ACT specified by the G-BA. b: Surgical castration or medical castration using treatment with LH-RH analogues or GnRH antagonists. c: Patients with brain metastasis or an ECOG/WHO Performance Status of > 2 were not investigated in the studies LATITUDE and STAMPEDE. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; LH-RH: luteinizing hormone-releasing hormone; mHSPC: metastatic hormone sensitive prostate cancer; WHO: World Health Organization		

[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].

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

2.2 Research question

The aim of the present report was the assessment of the added benefit of abiraterone acetate (hereinafter referred to as "abiraterone") in combination with prednisone/prednisolone (P) and androgen deprivation therapy (ADT) (hereinafter referred to as "abiraterone-P-ADT") in comparison with the ACT in patients with newly diagnosed high risk mHSPC.

For the benefit assessment of abiraterone, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of abiraterone

Research question	Therapeutic indication	ACT[a]
1	Patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC)	▪ conventional androgen deprivation therapy (ADT)[b] ▪ if applicable, in combination with a non-steroidal anti-androgen (flutamide or bicalutamide)

a: Presentation of the respective ACT specified by the G-BA.
b: Surgical castration or medical castration using treatment with LH-RH analogues or GnRH antagonists.
ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; LH-RH: luteinizing hormone-releasing hormone; mHSPC: metastatic hormone sensitive prostate cancer

The company concurred with the G-BA's specification on the ACT.

The assessment of the added benefit was conducted in comparison with the ACT and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

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 abiraterone (status: 17 October 2017)
- bibliographical literature search on abiraterone (last search on 11 October 2017)
- search in trial registries for studies on abiraterone (last search on 10 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on abiraterone (last search on 5 January 2018)

The check identified no additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
212082PCR3011 (LATITUDE[b])	Yes	Yes	No
STAMPEDE[c]	No	No[d]	Yes

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
c: The patient population with newly diagnosed metastatic disease of the treatment arms A and G of the study are relevant for the benefit assessment.
d: According to the available documents, the study provides financial support for the study, gives advice with regard to content and is involved in the production of the manuscript.
ADT: androgen deprivation therapy; P: prednisone/prednisolone: RCT: randomized controlled trial; vs.: versus

Study LATITUDE

The LATITUDE study, conducted by the company, was the basis for the extension of approval of abiraterone in newly diagnosed high risk mHSPC. It is used for the derivation of the added benefit in the present benefit assessment.

Study STAMPEDE

The STAMPEDE study was a third-party study, which, according to the information provided in the available documents, is financially supported by the company, and in which the company is involved as an advisor with regard to content. The assessment of this study was conducted on the basis of the published information on this study (see Section 2.6 of the present benefit assessment).

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LATITUDE	RCT, double-blind, parallel	Adult patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC)	Abiraterone + prednisone + ADT (N = 597) placebo + ADT (N = 602)	Screening: up to 28 days before randomization Treatment: until disease progression, unacceptable toxicity, death, non-conformity with the dosage, withdrawal of consent, or treatment discontinuation at the physician's decision Observation: outcome-specific, at most 60 months or until death, lost to follow-up, withdrawal of consent, or end of study	236 centres in 34 countries in Asia, Australia, Europe, Canada, Latin America, New Zealand and South Africa 1/2013–ongoing (open-label extension phase) Data cut-off: 31 Oct 2016	Primary: ▪ overall survival ▪ radiographic progression-free survival (rPFS) Secondary: symptomatic local progression, skeletal-related events, health status, pain, fatigue, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
STAMPEDE	RCT, open-label, parallel, platform trial	Adult patients with prostate cancer for whom long-term ADT is intended: ▪ with newly diagnosed, hormone sensitive[b], metastatic or lymph node-positive disease[c], or ▪ with high risk, locally advanced, non-metastatic disease with intended radiotherapy[c] ▪ pretreated with radiotherapy or surgery, with recurrent, locally advanced or metastatic disease[c]	Arms relevant for the assessment[d]: abiraterone + prednisone/ prednisolone + ADT (N = 960) ADT (N = 957) relevant patient population with metastatic (M1) disease[e]: abiraterone + prednisone/ prednisolone + ADT (n = 500) ADT (n = 502)	Screening: up to 8 weeks Treatment: until disease progression, unacceptable toxicity, withdrawal of consent or decision by the physician Observation: until death, withdrawal of consent	116 centres: 111 in the United Kingdom, 5 in Switzerland Total study: 2005–ongoing Relevant study arms: 11/2011–ongoing Data cut-off 10 Feb 2017	Primary: ▪ overall survival ▪ survival without treatment failure Secondary: skeletal-related events, health status, fatigue, pain, symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Patients were allowed ADT until at most 3 months before the start of the study. They are therefore considered to be hormone sensitive.
c: Patients with non-metastatic disease or with prior radiotherapy or surgery for the disease are not relevant for the assessment.
d: The STAMPEDE study is a study with one comparator arm (arm A) and different intervention arms. Only the comparison between arm A (ADT) and arm G (abiraterone + prednisone/prednisolone + ADT) is relevant for this assessment.
e: Including 35 (7.0%) patients with pretreatment in the abiraterone arm and 26 (5.2%) patients with pretreatment in the ADT arm; the other patients had newly diagnosed prostate cancer.

ADT: androgen deprivation therapy; AE: adverse event; mHSPC: metastatic hormone sensitive prostate cancer; n: number of patients in the relevant subpopulation; N: number of randomized patients; P: prednisone/prednisolone; RCT: randomized controlled trial; rPFS: radiographic progression-free survival; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study	Intervention	Comparison
LATITUDE	Abiraterone 1000 mg daily, orally[a] + prednisone 5 mg daily, orally[b] + ADT[c]	Abiraterone placebo daily, orally + prednisone placebo daily, orally + ADT[c]
	Pretreatment and concomitant treatment Permitted pretreatment: ▪ at most one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 28 days prior to the start of the study treatment ▪ ADT (surgical castration or administration of LH-RH agonists or antagonists) within 3 months before the start of the study, with or without concomitant administration of anti-androgens Concomitant treatment permitted: ▪ anti-androgens only for the treatment of the flare reaction[d] in the treatment with LH-RH agonists within the first 2 weeks after cycle day 1 ▪ opiates, analgesics for cancer-related pain[e] ▪ bisphosphonates and denosumab for the treatment of bone metastasis ▪ eplerenone for the treatment of mineralocorticoid side effects ▪ systemic glucocorticoids if clinically indicated in potentially fatal medical circumstances ▪ transfusions and haematopoietic growth factors Non-permitted concomitant treatment: ▪ any test medication except abiraterone ▪ other antineoplastic agents ▪ radiotherapy ▪ 5α reductase inhibitors ▪ chemotherapy ▪ immunotherapy	

(continued)

Table 7: Characteristics of the intervention – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Study	Intervention	Comparison
STAMPEDE	Abiraterone 1000 mg daily, orally[a] + prednisone/prednisolone 5 mg daily, orally[f] + ADT[g]	ADT[g]
	Pretreatment and concomitant treatment Permitted pretreatment: ▪ up to 3 months prior ADT (surgical castration or administration of LH-RH analogues), with or without concomitant administration of anti-androgens Non-permitted pretreatment: ▪ chemotherapy, surgery within 4 weeks prior to study inclusion Concomitant treatment permitted: ▪ any treatment deemed appropriate by the investigator (e.g. NSAIDs, bisphosphonates, vitamins) ▪ anti-androgens for the treatment of the flare reaction[d] in the treatment with LH-RH agonists	

a: Not to be taken together with a meal.
b: Dose increase to 10 mg daily in case of mineralocorticoid-related side effects.
c: Surgical castration (orchiectomy) following local guidelines or administration of LH-RH agonists; dose adjustments of the LH-RH agonists were possible to maintain testosterone levels below castration level (< 50 ng/dL).
d: Administration of LH-RH agonists leads to a short-term sharp increase in testosterone concentration in the blood. This is known as "flare reaction" and can be treated with additional administration of anti-androgens.
e: Not more than 3 weeks of oral treatment or 7 consecutive days of parenteral administration.
f: Dose increase to 10 mg daily in case of mineralocorticoid-related side effects, can be substituted by dexamethasone 0.5 mg daily in case of biochemical treatment failure.
g: Surgical castration (orchiectomy) or administration of LH-RH agonists or antagonists.
ADT: androgen deprivation therapy; LH-RH: luteinizing hormone-releasing hormone; NSAID: nonsteroidal anti-inflammatory drug; P: prednisone/prednisolone; RCT: randomized controlled trial; vs.: versus

LATITUDE

The LATITUDE study was a randomized, double-blind, placebo-controlled parallel-group study on the comparison of treatment with abiraterone in combination with prednisone and ADT (abiraterone-P-ADT) versus treatment with ADT plus additional administration of placebo.

The study included adult patients with newly diagnosed (within 3 months before randomization) high risk mHSPC. Presence of high risk mHSPC was defined by the presence of at least 2 of the 3 following high risk criteria: 1) Gleason score ≥ 8 in the primary tumour, 2) presence of ≥ 3 bone metastases, and 3) presence of visceral metastasis (excluding lymph node metastasis). The metastatic stage had to be documented by the presence of distant metastasis. The following patients were not included in the study: patients with brain metastasis,

metastatic recurrence, impaired cardiac, haematological, hepatic or renal function, adrenal disorders, uncontrolled hypertension or an ECOG Performance Status of > 2.

The maximum allowed pretreatment of the patients before the start of the study was one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 28 days prior to the first cycle of the study. In addition, patients were allowed prior ADT within 3 months before the start of the study.

A total of 1209 patients were included in the study until December 2014. Randomization was stratified by presence of visceral metastasis (yes/no) and ECOG Performance Status (0 or 1 versus 2). One study centre was excluded during the course of the study due to non-compliance with good clinical practice (GCP) guidelines. The data of the 10 patients treated in this study centre were not considered in the analysis of the study. Overall, data of 597 patients in the abiraterone arm and of 602 patients in the comparator arm were therefore included in the analysis of the study.

Treatment of the patients in the LATITUDE study followed the regimen described in Table 7 and concurred with the recommendations of the Summary of Product Characteristics (SPC) of abiraterone in the present therapeutic indication [3]. The choice of the adequate ADT for the patient (surgical or medical with LH-RH agonists) was at the treating physician's discretion. The treating physician could also adjust the dose of the LH-RH agonist to maintain the blood testosterone levels of the patient below castration level. Treatment was to be conducted until disease progression, occurrence of unacceptable toxicity, withdrawal of consent or decision by the treating physician.

The LATITUDE study was initiated on 25 January 2013 and was stopped prematurely following a positive result of a planned interim analysis for the outcomes "overall survival" and "progression-free survival" (data cut-off on 31 October 2016). In an open-label extension phase, patients still included in the study could be switched from the comparator arm to the abiraterone arm and receive the test medication until progression. Follow-up observation of the patients in the study after progression or discontinuation of treatment with abiraterone was up to 60 months in total or until the end of the study for the analysis of overall survival.

Co-primary outcomes of the study were overall survival and radiographic progression-free survival. Patient-relevant secondary outcomes were skeletal-related events, symptomatic local progression, pain, fatigue, health status, health-related quality of life, and AEs.

STAMPEDE

Study design

The STAMPEDE study is a randomized, open-label, multi-arm and multi-phase platform trial in advanced or metastatic prostate cancer on the comparison of different systemic drug therapies [4].

The STAMPEDE study includes patients with prostate cancer for whom long-term ADT is intended and whose disease concurs with one of the following 3 groups: 1) newly diagnosed disease with presence of distant metastasis or lymph node metastasis, 2) newly diagnosed disease with high risk locally advanced prostate cancer without distant metastasis or lymph node metastasis, 3) recurrent locally advanced or metastatic disease after prior radiotherapy and/or surgery. Only the patients in group 1 with distant metastasis were relevant for the present benefit assessment (see below under "Relevant patient population of the STAMPEDE study"). Patients from group 1 and 2 were allowed to have received ADT within 3 months before start of the study. Patients with brain metastasis, cardiovascular or cerebrovascular disease, impaired haematological, hepatic or renal function, or a WHO Performance Status of > 2 are not included in the study.

The STAMPEDE study started in 2005 with a total of 6 study arms. Arm A investigates ADT administration; the further arms B to F investigate different drugs and drug combinations consisting of zoledronic acid, docetaxel, or celecoxib. In 2011, arm G was added as comparator arm with abiraterone-P-ADT, in which both prednisone and prednisolone were allowed as concomitant treatment. Now the study has 4 additional study arms (H, J, K and L).

Only the comparison between study arm G (abiraterone-P-ADT) and study arm A (ADT, hereinafter referred to as "comparator arm") was relevant for the present benefit assessment. From November 2011 to January 2014, 1917 patients were randomized in a ratio of 1:1 to both parallel study arms: 960 patients were allocated to the abiraterone-P-ADT arm, and 957 patients to the comparator arm (ADT). Randomization is completed, whereas treatment and observation of the patients in these study arms are ongoing.

Treatment with abiraterone and prednisone/prednisolone in arm G of the STAMPEDE study follows the regimen described in Table 7 and concurs with the recommendations of the SPC of abiraterone in the present therapeutic indication [3]. ADT in the STAMPEDE study can be surgical or medical with LH-RH agonists or antagonists; the choice of ADT is at the treating physician's discretion. Treatment of the patients is until disease progression, unacceptable toxicity, or decision by the physician; follow-up observation after progression or discontinuation of treatment is until withdrawal of consent or death.

The analyses of the data cut-off from 10 February 2017 were considered for the present benefit assessment. Further data cut-offs for the relevant comparison have not been published yet.

Co-primary outcomes of the study were overall survival and survival without treatment failure. Patient-relevant secondary outcomes were (symptomatic) skeletal-related events, symptoms, health status, health-related quality of life, and AEs.

Only a specific patient population of the STAMPEDE study was relevant for the present benefit assessment. This is explained below.

Relevant patient population of the STAMPEDE study

In accordance with the approval requirements of abiraterone, only the data of the subpopulation of patients with newly diagnosed high risk hormone sensitive prostate cancer and distant metastasis were relevant for the present benefit assessment. The STAMPEDE study included both patients with distant metastasis and patients without distant metastasis, however. The company therefore presented a subpopulation of the STAMPEDE study, i.e. of the patients with distant metastasis (hereinafter referred to as "M1 patient population"). This subpopulation comprised 500 patients of the abiraterone-P-ADT arm (arm G) and 502 patients of the ADT arm (arm A) of the STAMPEDE study. Data for the M1 patient population are available in a full publication [5] and in a meta-analysis of the studies STAMPEDE and LATITUDE [6].

About 94% of the patients in the M1 patient population have a newly diagnosed prostate cancer with distant metastasis. The proportion of patients with already recurrent prostate cancer – which is therefore not concurring with the target population – was relatively low (7% in the abiraterone-P-ADT arm and 5.2% in the ADT arm) (see Table 10), raising no doubts about using the data of the total M1 patient population.

Fulfilment of the high risk criterion

Abiraterone was approved for use in high risk mHSPC. The SPC on abiraterone provides no specific definition of the high risk criterion, and no universally accepted definition, e.g. from guidelines, was available. The SPC of abiraterone refers to the criteria used in the LATITUDE study, however. Hence for the present benefit assessment, the high risk definition of the LATITUDE was used as decisive.

The LATITUDE study defined the high risk criterion as the presence of at least 2 of the 3 following risk factors:

- Gleason score ≥ 8 in the primary tumour
- presence of ≥ 3 bone metastases
- presence of visceral metastasis (excluding lymph node metastasis)

The proportion of patients who concur with the high risk definition of the approval study LATITUDE could not be inferred from the published patient characteristics of the M1 patient population of the STAMPEDE study. Table 8 therefore presents a comparison of the patient characteristics of the LATITUDE study and of the M1 patient population of the STAMPEDE study.

Table 8: Comparison of high risk factors – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study Characteristics Category	LATITUDE N = 1199	STAMPEDE (M1 patient population) N = 1002
Gleason score, n (%)		
≤ 7	29 (2.4)[a]	234 (23.4)[a]
8–10	1170 (97.6)[a]	737 (73.6)[a]
Unknown	0 (0)	31 (3.1)[a]
Bone metastases, n (%)		
0	13 (1.1)	120 (12)[a]
1–2	15 (1.3)	ND
3–10	410 (34.2)	ND
11–20	206 (17.2)	ND
> 20	555 (46.3)	ND
≥ 3	1171 (97.7)[a]	ND
Location of metastases, n (%)		
Bone	1165 (97.4)	882 (88.0)[a]
Liver	62 (5.2)	15 (1.5)[a]
Lung	145 (12.1)	42 (4.2)[a]
Lymph nodes	570 (47.7)	292 (29.1)[a]
Visceral total	228 (19.0)	ND
Other[b]	ND	49 (4.9)[a]

a: Data on the patient number and on percentages are based on calculations by the Institute using information provided in Module 4 A.
b: All other locations excluding bone, liver, lung and lymph nodes.
ADT: androgen deprivation therapy; n: number of patients in the category; N: number of randomized patients; ND: no data; P: prednisone/prednisolone; RCT: randomized controlled trial; vs.: versus

Fulfilment of the criterion of the high risk mHSPC for the study population of the LATITUDE study mainly resulted from the 2 criteria of a large number of patients with ≥ 3 bone metastases (1171 of 1199 [97.7%] patients) and/or a Gleason score of ≥ 8 (1170 of 1199 [97.6%] patients).

With 882 of 1002 (88%) patients, the proportion of patients with presence of bone metastasis was also very high in the M1 patient population of the STAMPEDE study; information on the number of bone metastases per patient was missing, however.

With 737 of 1002 (73.6%) patients, the proportion of patients with a Gleason score of ≥ 8 was also relatively high overall in the M1 patient population of the STAMPEDE study, but was relatively low in comparison with the LATITUDE study (97.6%). The patient populations of the LATITUDE study and the M1 patient population of the STAMPEDE study were still considered to be sufficiently comparable regarding this characteristic, particularly as an analysis conducted by the Institute for the outcome “overall survival” in the LATITUDE study

and in the M1 patient population of the STAMPEDE study showed no effect modification for the characteristic "Gleason score" (≥ 8 versus < 8, see Figure 1 in Appendix A of the full dossier assessment).

Inclusion of the studies in the derivation of the added benefit

Despite the described uncertainties, the M1 patient population of the STAMPEDE study was overall a sufficient representation of the target population and was included in the present benefit assessment in addition to the LATITUDE study. In the comparison of both studies, the patients of the LATITUDE study concurred more closely with the target population of the present benefit assessment than the M1 patient population of the STAMPEDE study, however.

In the present benefit assessment, the results of the LATITUDE study and of the M1 patient population of the STAMPEDE are pooled in a meta-analysis. In principle, the results of the LATITUDE study and of the STAMPEDE study were considered jointly. In case of decisive heterogeneity of the results, the LATITUDE study was used primarily for conclusions on benefit because the patient population of the LATITUDE study was more similar to the target population.

Follow-up

Table 9 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study **Outcome category** **Outcome**	**Planned follow-up observation**
LATITUDE	
Mortality	
Overall survival	After end of treatment every 4 months up to 60 months in total, or until death, withdrawal of consent, lost to follow-up or end of study
Morbidity	
Health status	From start of the study monthly for the first 13 treatment intervals of 28 days, then every 2 months; after end of treatment every 4 months until 12 months in total
Other morbidity outcomes	From start of the study monthly for the first 13 treatment intervals of 28 days, then every 2 months, until 30 days after end of treatment
Health-related quality of life	From start of the study monthly for the first 13 treatment intervals of 28 days, then every 2 months, until 30 days after end of treatment
Side effects	Continuously from start of the study until 30 days after end of treatment
STAMPEDE	
Mortality	
Overall survival	From start of the study observation every 6 weeks for 6 months, then every 12 weeks until 2 years, then every 6 months until 5 years, then yearly until withdrawal of consent
Morbidity	From start of the study observation every 6 weeks for 6 months, then every 12 weeks until 2 years, then every 6 months until 5 years, then yearly until withdrawal of consent
Health-related quality of life	From start of the study observation every 6 weeks for 6 months, then every 12 weeks until 2 years, then every 6 months until 5 years, then yearly until withdrawal of consent
Side effects	Continuously from start of the study

ADT: androgen deprivation therapy; P: prednisone/prednisolone: RCT: randomized controlled trial; vs.: versus

In the LATITUDE study, the observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication plus 30 days or plus 1 year for health status. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for overall survival.

The patients in the STAMPEDE study are observed across outcomes until withdrawal of consent or death. Planned observations are conducted from the start of the study every 6 weeks for 6 months, then every 12 weeks for 2 years, then every 6 months for up to 5 years, and then once a year. Side effects are recorded from the start of the study for at least 2 years.

Patient characteristics

Table 10 shows the characteristics of the patients in the studies included.

Table 10: Characteristics of the study population – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study **Characteristics** **Category**	**Abiraterone-P-ADT**	**ADT[a]**
LATITUDE	N[b] = 597	N[b] = 602
Age [years], median [min; max]	68 [38; 89]	67 [33; 92]
Region, n (%)		
Eastern Europe	214 (35.8)	217 (36.0)
Western Europe	155 (26.0)	162 (26.9)
Asia	124 (20.8)	121 (20.1)
Rest of the world	104 (17.4)	102 (16.9)
Time between diagnosis and first study medication [months]		
Median [min; max]	1.8 [0; 3]	2.0 [0; 4]
Gleason score at diagnosis, n (%)		
< 7	4 (0.7)	1 (0.2)
7	9 (1.5)	15 (2.5)
8	267 (44.7)	281 (46.7)
9	280 (46.9)	264 (43.9)
10	37 (6.2)	41 (6.8)
Stage of metastasis, n (%)		
M1[c]	597 (100)	602 (100)
Location of metastases, n (%)		
Bone	580 (97.3)	585 (97.5)
Liver	32 (5.4)	30 (5.0)
Lung	73 (12.2)	72 (12.0)
Lymph nodes	283 (47.5)	287 (47.8)
Prostate tissue	151 (25.3)	154 (25.7)
Visceral tissue	18 (3.0)	13 (2.2)
Soft tissue	9 (1.5)	15 (2.5)
Other	2 (0.3)	0 (0.0)
Number of bone metastases, n (%)		
0	6 (1.0)	7 (1.2)
1–2	5 (0.8)	10 (1.7)
3–10	202 (33.8)	208 (34.6)
11–20	109 (18.3)	97 (16.1)
> 20	275 (46.1)	280 (46.5)

(continued)

Table 10: Characteristics of the study population – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Study Characteristics Category	Abiraterone-P-ADT	ADT[a]
ECOG Performance Status, n (%)		
0	326 (54.6)	331 (55.0)
1	245 (41.0)	255 (42.4)
2	26 (4.4)	16 (2.7)
Worst pain (BPI-SF Item 3), n (%)[d]		
0–1	284 (49.8)	288 (49.7)
2–3	123 (21.6)	137 (23.7)
≥ 4	163 (28.6)	154 (26.6)
Median [min; max]	2.0 [0; 10]	2.0 [0; 10]
Mean (SD)	2.2 (2.5)	2.2 (2.4)
Patients with prior therapy of the prostate cancer before start of study, n (%)	560 (93.8)	560 (93.0[e])
Type of prior therapy, n (%)		
Surgery	22 (3.7)	23 (3.8)
Radiotherapy	19 (3.2)	26 (4.3)
Hormonal therapy[f]	559 (93.6)	558 (92.7)
LH-RH-based therapy[g]	449 (75.2)	450 (74.8)
Orchiectomy	73 (12.2)	71 (11.8)
Anti-androgens	373 (62.5)	371 (61.6)
Other[h]	7 (1.2)	10 (1.7)
Treatment discontinuation, n (%)	340 (57.0)	490 (81.4)
Study discontinuation, n (%)	ND	ND
STAMPEDE	N[i] = 500	N[i] = 502
Age [years], median [min; max]	67 [42; 85]	67 [39; 84]
Region, n (%)		
Western Europe[j]	500 (100)	502 (100)
Time since diagnosis [days]		
Median [min; max]	2.5 [0; 177]	2.3 [0; 160]
Gleason score at diagnosis, n (%)		
< 7	115 (23.0)	119 (23.7)
8 to 10	364 (72.8)	373 (74.3)
Unknown	21 (4.2)	10 (2.0)
Stage of metastasis, n (%)		
M1[c]	500 (100)[e]	502 (100)[e]
Stage of disease, n (%)		
Newly diagnosed	465 (93.0)	476 (94.8)
Recurrent disease	35 (7.0)	26 (5.2)

(continued)

Table 10: Characteristics of the study population – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Study **Characteristics** **Category**	**Abiraterone-P-ADT**	**ADT[a]**
Location of metastases, n (%)		
Bone	434 (86.8)	448 (89.2)
Liver	7 (1.4)	8 (1.6)
Lung	21 (4.2)	21 (4.2)
Lymph nodes	142 (28.4)	150 (29.9)
Prostate tissue	ND	ND
Visceral tissue	ND	ND
Soft tissue	ND	ND
Other	23 (4.6)	26 (5.2)
Number of bone metastases, n (%)		
0	ND	ND
1–2	ND	ND
3–10	ND	ND
11–20	ND	ND
> 20	ND	ND
WHO Performance Status, n (%)		
0	374 (74.8)	370 (73.7)
1	119 (23.8)	125 (24.9)
2	7 (1.4)	7 (1.4)
Worst pain (BPI-SF Item 3), n (%)	ND	ND
Patients with prior therapy of the prostate cancer before start of study, n (%)	ND	ND
Type of prior therapy		
Surgery	ND	ND
Radiotherapy	ND	ND
Hormonal therapy[f, k]	ND	ND
LH-RH-based therapy[g]	496 (99.2)	495 (98.6)
Orchiectomy	3 (0.6)	3 (0.6)
Bicalutamide/anti-androgens alone	0 (0)	1 (0.2)
Dual androgen blockade[l]	1 (0.2)	3 (0.6)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

(continued)

Table 10: Characteristics of the study population – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

a: LATITUDE study: ADT + placebo for abiraterone and prednisone; STAMPEDE study: ADT.
b: Number of randomized patients; values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: TNM classification system: M1 = disease with distant metastasis.
d: n = 570 in the abiraterone-P-ADT arm, and n = 579 in the ADT arm.
e: Institute's calculation.
f: Patients could receive several medications at the same time.
g: Administration of LH-RH agonists or antagonists.
h: Including oestrogens and glucocorticoids.
i: Number of randomized patients in the relevant subpopulation; values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
j: Study centres are only in Western Europe (Great Britain and Switzerland).
k: It could not be inferred from the data published in Rydzewska 2017 whether this is a prior or a concomitant therapy or whether these can be equated.
l: Combination of LH-RH-based therapy and anti-androgens.
ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; ECOG: Eastern Cooperative Oncology Group; F: female; M: male; number of patients in the category; N: number of randomized patients; ND: no data; P: prednisone/prednisolone; RCT: randomized controlled trial; SD: standard deviation; TNM: tumour-node-metastasis; vs.: versus; WHO: World Health Organization

Within the studies, the demographic and clinical characteristics of the patients are largely balanced between the individual study arms. There are minor differences between the studies.

At enrolment, the median age of the patients was about 67 years, and the median time from diagnosis of the metastatic prostate cancer until start of the study was about 2 months. The proportion of patients with a Gleason score of ≥ 8, as measure of the grade of the tumour cells in the primary tumour, was higher in the LATITUDE study (about 97%) than in the STAMPEDE study (about 76%). The proportion of patients with bone metastasis was also higher in the LATITUDE study (about 97%) than in the STAMPEDE study (about 88%). Almost all patients in both studies were in good or very good general condition, as measured with the ECOG (LATITUDE) or the WHO (STAMPEDE) Performance Status. Whereas about 49% of the patients in the LATITUDE study were not affected by very bad pain at diagnosis, no corresponding information was available for the STAMPEDE study.

Compared with the patient population in the LATITUDE study, the disease appeared to be less advanced in the patients in the STAMPEDE study.

Table 11 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study **Duration of the study phase** **Outcome category**	**Abiraterone-P-ADT**	**ADT[a]**
LATITUDE	N = 597	N = 602
Treatment duration [months]		
Median [min; max]	24.0 [0.1; 43.0]	14.3 [0.7; 42.6]
Mean (SD)	22.3 (11.5)	16.1 (10.5)
Observation period [months]		
Overall survival		
Median [min; max]	30.9 [0.1; 43.5]	29.7 [1.4; 43.5]
Mean (SD)	26.2 (9.9)	23.6 (10.1)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND
STAMPEDE	N = 500	N = 502
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Observation period [months][b]		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a: LATITUDE study: ADT + placebo for abiraterone and prednisone; STAMPEDE study: ADT.

b: Median observation duration for overall survival – and hence probably also for all other outcomes – in both arms together = 41 months.

ADT: androgen deprivation therapy; N: number of randomized patients; ND: no data;
P: prednisone/prednisolone; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the LATITUDE study, the median treatment duration for patients in the intervention arm differed markedly from the comparator arm (24.0 versus 14.3 months). The median observation period for the outcome "overall survival", however, was comparable between both study arms (30.9 versus 29.7 months) because this outcome was followed-up also after the end of treatment up to 60 months in total or until death. No information on the observation periods was available for the further outcomes of the categories "morbidity", "health-related quality of life" and "side effects". In contrast to the outcome "overall survival", it is assumed for these outcomes that not only the treatment durations, but also the observation periods differed between the study arms because of the differences in treatment duration between the study arms and the shorter follow-up observation periods in comparison with overall survival (30 days and 12 months). Correspondingly, for all outcomes, except for the outcome "discontinuation due to AEs",

analyses based on relative risks are not informative for the present assessment. The assessment was therefore based on event time analyses.

No information on the actual treatment duration and observation period for both treatment arms of the relevant subpopulation was available for the STAMPEDE study. However, since the observation period in this study was not based on disease progression, the actual observation periods are probably comparable between both arms. Calculated across both arms, the median observation period for overall survival and hence for all outcomes was 41 months at the data cut-off considered.

Hence overall, the observation period was notably longer for the patients in the STAMPEDE study (41 months) than in the LATITUDE study (30.9 months and 29.7 months for overall survival, and an estimated 25.0 and 15.3 months for all other outcomes).

Risk of bias

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
LATITUDE	Yes	Yes	Yes	Yes	Yes	Yes	Low
STAMPEDE	Yes	Yes	No	No	Yes	No[a]	Low

a: Incomplete reporting.
ADT: androgen deprivation therapy; P: prednisone/prednisolone: RCT: randomized controlled trial; vs.: versus

The risk of bias at study level for the LATITUDE study was rated as low. This concurs with the company's assessment.

For the STAMPEDE study, reporting was incomplete. Without further explanation, all planned analyses on the outcomes "EQ-5D-5L" and "EORTC QLQ-C30 and PR25" were missing. It is unclear whether this non-reporting of the results was event-driven. Despite the missing data, the risk of bias at study level was rated as low. This concurs with the assessment of the company, which also rated the risk of bias at study level as low for the STAMPEDE study, without addressing the unreported results of the patient questionnaires mentioned above.

The problem of the missing data was considered for the specific outcomes and in the derivation of the added benefit. Limitations resulting from the open-label study design of the STAMPEDE study, if relevant, are also described with the outcome-specific risk of bias (Section 2.4).

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptomatic local disease progression
  - skeletal-related events
  - health status (recorded with the EQ-5D VAS)
  - pain (recorded with the BPI-SF questionnaire in the LATITUDE study and with the pain symptom scale of the EORTC QLQ-C30 questionnaire in the STAMPEDE study)
  - fatigue (recorded with the BFI questionnaire in the LATITUDE study and with the fatigue symptom scale of the EORTC QLQ-C30 questionnaire in the STAMPEDE study)
  - further symptom outcomes (recorded with the questionnaires EORTC QLQ-C30 and PR25)
- Health-related quality of life
  - health-related quality of life (recorded with the questionnaires FACT-P and EORTC QLQ-C30)
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3–4)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

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

Table 13: Matrix of outcomes – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study	Outcomes														
	Overall survival	Morbidity: symptomatic local disease progression[a]	Morbidity: skeletal-related events[b]	Morbidity: health status (EQ-5D-5L)	Morbidity: pain (BPI-SF and EORTC QLQ-C30)	Morbidity: fatigue (BFI and EORTC QLQ-C30)	Health-related quality of life (FACT-P)	Morbidity and health-related quality of life (EORTC QLQ-C30/PR25)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Fluid retention/oedema[c]	Cardiac failure[d]	Ischaemic heart disease[e]	Further common AEs[f]
LATITUDE	Y	Y	Y	Y	Y[g]	Y[h]	Y	N[i]	Y	Y	Y	Y	N[j]	N[j]	Y
STAMPEDE	Y	N[i]	Y	N[k]	N[l]	N[l]	N[i]	N[k]	N[k]	N[k]	N[m]	N[n]	N[n]	N[n]	N[m]

a: Urethral or bladder outlet obstruction requiring medical treatment.
b: Fractures, spinal cord compression, palliative radiation or surgery to bone.
c: AEs predefined in the study, corresponding to the MedDRA SMQ haemodynamic oedema, effusions and fluid overload.
d: Subgrouping of the predefined AE cardiac disorders using the MedDRA SMQ cardiac failure.
e: Subgrouping of the predefined AE cardiac disorders using the aggregate MedDRA SMQs ischaemic heart disease and myocardial infarction.
f: The following events are considered (MedDRA coding): hypokalaemia (PT, CTCAE grade 3–4), ALT increased (PT, CTCAE grade 3–4), AST increased (PT, CTCAE grade 3–4).
g: Outcome only recorded with the BPI-SF.
h: Outcome only recorded with the BFI.
i: Outcome not recorded.
j: No usable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.
k: Outcome recorded, but not reported.
l: Outcome was only recorded with the EORTC QLQ-C30; but no results are reported.
m: Outcome recorded, but not reported for the relevant subpopulation.
n: Separate analyses for these outcomes were not planned for the STAMPEDE study.

ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BFI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACT-P: Functional Assessment of Cancer Therapy-Prostate; MedDRA: Medical Dictionary for Regulatory Activities; N: no; P: prednisone/prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus; Y: yes

2.4.2 Risk of bias

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

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study	Study level	Outcomes														
		Overall survival	Morbidity: symptomatic local disease progression[a]	Morbidity: skeletal-related events[b]	Morbidity: health status (EQ-5D-5L)	Morbidity: pain (BPI-SF and EORTC QLQ-C30)	Morbidity: fatigue (BFI and EORTC QLQ-C30)	Health-related quality of life (FACT-P)	Morbidity and health-related quality of life (EORTC QLQ-C30/PR25)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Fluid retention/oedema[c]	Cardiac failure[d]	Ischaemic heart disease[e]	Further common AEs[f]
LATITUDE	L	L	H[g]	H[g]	H[g]	H[h]	H[h]	H[g]	–[i]	H[g]	L	H[g]	H[g]	–[j]	–[j]	H[g]
STAMPEDE	L	L	–[i]	L	–[k]	–[l]	–[l]	–[i]	–[k]	–[k]	–[k]	–[m]	–[n]	–[n]	–[n]	–[m]

a: Urethral or bladder outlet obstruction requiring medical treatment.
b: Fractures, spinal cord compression, palliative radiation or surgery to bone.
c: AEs predefined in the study, corresponding to the MedDRA SMQ haemodynamic oedema, effusions and fluid overload.
d: Subgrouping of the predefined AE cardiac disorders using the MedDRA SMQ cardiac failure.
e: Subgrouping of the predefined AE cardiac disorders using the aggregate MedDRA SMQs ischaemic heart disease and myocardial infarction.
f: The following events are considered (MedDRA coding): hypokalaemia (PT, CTCAE grade 3–4), ALT increased (PT, CTCAE grade 3–4), AST increased (PT, CTCAE grade 3–4).
g: Potential informative censoring in different observation periods.
h: Outcome "pain": recording with BPI-SF, outcome "fatigue": recording with BFI; incomplete observations: large and very different proportion of patients between the treatment groups (abiraterone-P-ADT arm 35% vs. ADT arm 61.3%) for whom observation was stopped in the course of the study due to disease progression (increasingly different response rates in the treatment arms); for the operationalization "worst pain" (BPI-SF Item 3): potential informative censoring in different observation periods.
i: Outcome not recorded.
j: No usable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.
k: Outcome recorded, but not reported.
l: Outcome was only recorded with the EORTC QLQ-C30; but no results are reported.
m: Outcome recorded, but not reported for the relevant subpopulation.
n: Outcome not analysed.

ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BFI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; P: prednisone/prednisolone; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus

The risk of bias for the outcome “overall survival” (LATITUDE and STAMPEDE) at outcome level was rated as low. This concurs with the company’s assessment.

Treatment duration and observation period for the LATITUDE study were markedly shortened and, in addition, differed between the treatment groups. Furthermore, the shortening of the observation period, which was of different extent in the treatment groups, was based on disease progression, which makes a notable extent of informative censoring in survival time analyses possible. For these reasons, the risk of bias was rated as high for all further outcomes of the categories of morbidity, health-related quality of life, and side effects (except discontinuation due to AEs).

This deviates from the assessment of the company, which included the problem of different observation periods due to informative censorings in the assessment of the risk of bias only for the outcomes in the category of side effects.

The risk of bias was rated as low for the outcome “symptomatic skeletal-related events” for the STAMPEDE study, but not for the LATITUDE study (see above). This concurs with the company’s assessment. For further outcomes (except overall survival), no results relevant for the present benefit assessment were presented for the study.

Final assessment of the certainty of conclusions

The assessment of the risk of bias of the outcomes was included in the assessment of the results of individual outcomes. It was taken into account whether the results were available in only one or in both studies. In addition, as described in Section 2.3.1, the patients in the LATITUDE study correspond more closely to the target population of the present benefit assessment. In case of important heterogeneity of the results, an added benefit was therefore derived primarily from this study. This resulted in the following assessment for the present benefit assessment:

Based on the available data, at most proof, e.g. of an added benefit, can be derived for the outcome “overall survival” and “skeletal-related events”, at most an indication for the outcome “discontinuation due to AEs”, and at most a hint for all other outcomes.

2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of abiraterone-P-ADT with ADT in adult patients with newly diagnosed high risk mHSPC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. Meta-analyses conducted by the Institute can be found in Appendix A of the full dossier assessment. Kaplan-Meier curves on the outcomes analysed using event time analyses can be found in Appendix B of the full dossier assessment. Results on common AEs of the LATITUDE study are presented in Appendix C of the full dossier assessment. For the STAMPEDE study, there were no systematic analyses for AEs that occurred in the relevant M1 patient population.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Outcome category Outcome Study	Abiraterone-P-ADT N	Median time to event in months [95% CI] Patients with event n (%)	ADT[a] N	Median time to event in months [95% CI] Patients with event n (%)	Abiraterone-P-ADT vs. ADT HR [95% CI]; p-value
Mortality					
Overall survival					
LATITUDE	597	NA [NA; NA] 169 (28.3)	602	34.7 [33.05; NA] 237 (39.4)	0.62 [0.51; 0.76]; < 0.001[b]
STAMPEDE	500	NA [NA; NA] 150 (30.0)	502	48 [NA; NA] 218 (56.0)	0.61 [0.49; 0.75]; 0.001[c]
Total[d]					0.62 [0.53; 0.71]; < 0.001[e]
Morbidity					
Symptomatic local disease progression					
LATITUDE	597	NA [NA; NA] 33 (5.5)	602	NA [NA; NA] 37 (6.1)	0.67 [0.42; 1.08]; 0.101[b, f]
STAMPEDE	Outcome not recorded				
Skeletal-related events (composite outcome)					
LATITUDE	597	NA [NA; NA] 98 (16.4)	602	NA [NA; NA] 125 (20.8)	0.70 [0.54; 0.92]; 0.009[b]
STAMPEDE[g]	500	NA [NA; NA] 102 (20.4)[e, f]	502	NA [NA; NA] 184 (36.7)[e, f]	0.45 [0.36; 0.58][c]; ND
Total[e]	Heterogeneity[e] Q = 6.01; df = 1; p = 0.014; I^2 = 83.4%				
Component of the composite outcome (LATITUDE)					
Clinical or pathological fracture	597	NA [NA; NA] 28 (4.7)	602	NA [NA; NA] 25 (4.2)	1.19 [0.67; 2.11]; 0.545[b]
Spinal cord compression	597	NA [NA; NA] 22 (3.7)	602	NA [NA; NA] 24 (4.0)	0.84 [0.47; 1.50]; 0.562[b]
Palliative radiation to bone	597	NA [NA; NA] 67 (11.2)	602	NA [NA; NA] 99 (16.4)	0.60 [0.44; 0.82]; 0.001[b]
Surgery to bone	597	NA [NA; NA] 4 (0.7)	602	NA [NA; NA] 5 (0.8)	0.74 [0.20; 2.77]; 0.656[b]
Symptoms (EORTC QLQ-C30 and PR25)[h]					
LATITUDE	Outcome not recorded				
STAMPEDE	Outcome recorded, but not reported				

(continued)

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Outcome category Outcome Study	Abiraterone-P-ADT N	Abiraterone-P-ADT Median time to event in months [95% CI] Patients with event n (%)	ADT[a] N	ADT[a] Median time to event in months [95% CI] Patients with event n (%)	Abiraterone-P-ADT vs. ADT HR [95% CI]; p-value
Health status (EQ-5D VAS) – time to deterioration by ≥ 7 points					
LATITUDE	597	9.2 [ND] 365 (61.1)	602	5.6 [ND] 405 (67.3)	0.81 [0.70; 0.94]; 0.004[i]
STAMPEDE	Outcome recorded, but not reported				
Health status (EQ-5D VAS) – time to deterioration by ≥ 10 points					
LATITUDE	597	12.9 [ND] 343 (57.5)	602	8.3 [ND] 371 (61.6)	0.83 [0.72; 0.97]; 0.015[i]
STAMPEDE	Outcome recorded, but not reported				
Worst Pain (BPI-SF Item 3) – time to deterioration by ≥ 2 points					
LATITUDE	597	NA [NA; NA] 173 (29.0)	602	NA [NA; NA] 228 (37.9)	0.63 [0.52; 0.77]; < 0.001[b]
STAMPEDE	Outcome not recorded				
Pain (EORTC QLQ-C30 pain scale)					
LATITUDE	Outcome not recorded				
STAMPEDE	Outcome recorded, but not reported				
Health-related quality of life					
Recorded with FACT-P					
LATITUDE					
Total score, deterioration by ≥ 10 points	597	12.9 [ND] 347 (58.1)	602	8.3 [ND] 369 (61.3)	0.85 [0.74; 0.99]; 0.035[i]
PCS, deterioration by ≥ 3 points	597	8.3 [ND] 375 (62.8)	602	5.6 [ND] 404 (67.1)	0.81 [0.70; 0.93]; 0.003[i]
Physical well-being (PWB), deterioration by ≥ 3 points	597	14.4 [ND] 343 (57.5)	602	7.4 [ND] 385 (64.0)	0.75 [0.65; 0.87]; < 0.001[i]
Social well-being (SFWB), deterioration by ≥ 3 points	597	3.8 [ND] 394 (66.0)	602	5.5 [ND] 376 (62.5)	1.06 [0.92; 1.23]; 0.394[i]
Emotional well-being (EWB), deterioration by ≥ 3 points	597	16.1 [ND] 325 (54.4)	602	10.2 [ND] 323 (53.7)	0.92 [0.79; 1.08]; 0.311[i]

(continued)

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Outcome category Outcome Study	Abiraterone-P-ADT N	Abiraterone-P-ADT Median time to event in months [95% CI] Patients with event n (%)	ADT[a] N	ADT[a] Median time to event in months [95% CI] Patients with event n (%)	Abiraterone-P-ADT vs. ADT HR [95% CI]; p-value
Functional well-being (FWB), deterioration by ≥ 3 points	597	7.4 [ND] 385 (64.5)	602	5.5 [ND] 396 (65.8)	0.89 [0.78; 1.03]; 0.117[i]
STAMPEDE	Outcome not recorded				
Recorded with EORTC QLQ-C30[j]					
LATITUDE	Outcome not recorded				
STAMPEDE	Outcome recorded, but not reported				
Side effects					
AEs (supplementary information)					
LATITUDE	597	1.1 [ND] 558 (93.5)	602	1.4 [ND] 557 (92.5)	–
STAMPEDE	ND				
SAEs					
LATITUDE	597	NA [ND] 165 (27.6)	602	NA [ND] 146 (24.3)	0.85 [0.68; 1.07]; 0.169[j]
STAMPEDE	ND				
Severe AEs (CTCAE grade 3–4)					
LATITUDE	597	13.9 [ND] 374 (62.6)	602	20.2 [ND] 287 (47.7)	1.26 [1.08; 1.48]; 0.003[j]
STAMPEDE	ND				
Discontinuation due to AEs					
LATITUDE	597	NA [ND] 73 (12.2)	602	NA [ND] 61 (10.1)	RR: 1.21 [0.88; 1.66]; 0.272
STAMPEDE	ND				
Specific AEs					
Fluid retention/oedema					
LATITUDE	597	NA [ND] 74 (12.4)	602	NA [ND] 68 (11.3)	0.96 [0.69; 1.33]; 0.783[k]
STAMPEDE	ND				
Cardiac failure					
LATITUDE	No usable data[l]				
STAMPEDE	ND				

(continued)

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

Outcome category Outcome Study	Abiraterone-P-ADT N	Abiraterone-P-ADT Median time to event in months [95% CI] Patients with event n (%)	ADT[a] N	ADT[a] Median time to event in months [95% CI] Patients with event n (%)	Abiraterone-P-ADT vs. ADT HR [95% CI]; p-value
Ischaemic heart disease					
LATITUDE				No usable data[l]	
STAMPEDE				ND	
Hypokalaemia (CTCAE grade 3–4)					
LATITUDE	597	NA [ND] 62 (10.4)	602	NA [ND] 8 (1.3)	6.32 [3.02; 13.21]; < 0.001[k]
STAMPEDE				ND	
Alanine aminotransferase (ALT) increased (CTCAE grade 3–4)					
LATITUDE	597	NA [ND] 33 (5.5)	602	NA [ND] 8 (1.3)	3.99 [1.84; 8.65]; < 0.001[k]
STAMPEDE				ND	
Aspartate aminotransferase (AST) increased (CTCAE grade 3–4)					
LATITUDE	597	NA [ND] 26 (4.4)	602	NA [ND] 9 (1.5)	2.72 [1.27; 5.80]; 0.010[k]
STAMPEDE				ND	

(continued)

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

a: LATITUDE study: ADT + placebo for abiraterone and prednisone; STAMPEDE study: ADT.
b: HR and 95% CI from Cox model stratified by visceral metastasis (yes/no) and ECOG Performance Status (0/1 versus 2); p-value from stratified log-rank test.
c: HR and 95% CI from Cox model stratified by age at randomization, presence of metastasis, planned radiotherapy, lymph node metastasis, WHO Status, long-term treatment with analgesics.
d: From meta-analysis with fixed effect.
e: Institute's calculation.
f: Symptomatic local progression: information is from Module 4 A (stratified analysis) and deviates from the information provided in the study documents, for which it was not clearly designated whether they are also stratified analyses; skeletal-related events: information is from James 2017 [5] and deviates from Module 4 A, which is probably due to a transcription error by the company.
g: Defined as symptomatic skeletal-related events: pathological fracture, spinal cord compression or necessity of palliative radiation or surgery due to bone pain; no results available for individual components.
h: The EORTC QLQ-C30 contains 8 relevant morbidity outcomes, 4 of which are symptom scales. In addition to the EORTC QLQ-C30, the additional module QLQ-PR25, which contains 4 further prostate cancer-specific symptom scales and 2 functional scales, was recorded in the STAMPEDE study.
i: HR, 95% CI and p-value from Cox model stratified by visceral metastasis (yes/no) and ECOG Performance Status (0/1 versus 2).
j: The outcome category health-related quality of life of the EORTC QLQ-C30 contains 5 functional scales and one scale on global health status.
k: HR, 95% CI and p-value from unstratified Cox model.
l: No event time analyses available.

ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D: European Quality of Life-5 Dimensions; EWB: emotional well-being; FACT-P: Functional Assessment of Cancer Therapy-Prostate; FWB: functional well-being; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; P: prednisone/prednisolone; PCS: prostate-specific subscale of the FACT-P; PWB: physical well-being; RCT: randomized controlled trial; SAE: serious adverse event; SFWB: social/family well-being; VAS: visual analogue scale; vs.: versus; WHO: World Health Organization

Table 16: Results (morbidity, continuous) – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Outcome category Outcome Study	Abiraterone-P-ADT N[b]	Values at study start mean (SD)	Change at data cut-off mean[c] (SE)	ADT[a] N[b]	Values at study start mean (SD)	Change at data cut-off mean[c] (SE)	Abiraterone-P-ADT vs. ADT MD [95% CI]; p-value[c]
Morbidity							
Pain intensity (BPI-SF Items 3–6)[d] (additional information)							
LATITUDE	563	1.64 (1.78)	−0.15 (0.05)	575	1.65 (1.81)	0.22 (0.05)	−0.37 [−0.52; −0.22]; < 0.001 Hedges' g: −0.28 [−0.40; −0.17]
STAMPEDE	Outcome not recorded						
Pain interference (BPI-SF Items 9 a–g)[d]							
LATITUDE	563	1.42 (1.92)	−0.14 (0.06)	575	1.44 (2.03)	0.19 (0.06)	−0.34 [−0.49; −0.18]; < 0.001 Hedges' g: −0.25 [−0.36; −0.13]
STAMPEDE	Outcome not recorded						
Fatigue intensity (BFI Items 1−3)[d] (additional information)							
LATITUDE	No usable data						
STAMPEDE	Outcome not recorded						
Worst fatigue (BFI Item 3)[d]							
LATITUDE	562	2.13 (2.53)	−0.25 (0.07)	574	2.21 (2.55)	0.09 (0.07)	−0.34 [−0.52; −0.15] < 0.001 Hedges' g: −0.21 [−0.33; −0.09]
STAMPEDE	Outcome not recorded						
Fatigue interference (BFI Items 4 a–f)[d]							
LATITUDE	562	1.35 (1.97)	−0.12 (0.06)	574	1.36 (1.95)	0.16 (0.06)	−0.28 [−0.43; −0.12] < 0.001 Hedges' g: −0.21 [−0.33; −0.09]
STAMPEDE	Outcome not recorded						
Fatigue (EORTC QLQ-C30 fatigue scale)							
LATITUDE	Outcome not recorded						
STAMPEDE	Outcome recorded, but not reported						

(continued)

Table 16: Results (morbidity, continuous) – RCT, direct comparison: abiraterone-P-ADT vs. ADT (continued)

a: LATITUDE study: ADT + placebo for abiraterone and prednisone; STAMPEDE study: ADT.
b: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
c: Effect, CI and p-value: mixed-effects model repeated measures (MMRM).
d: A negative change compared with the start of the study indicates improvement; a negative effect estimate therefore indicates an advantage of abiraterone-P-ADT.
ADT: androgen deprivation therapy; BFI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; P: prednisone/prednisolone; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs: versus

Mortality

Overall survival

The meta-analysis (see Figure 2 in Appendix A of the full dossier assessment) showed a statistically significant difference in favour of abiraterone-P-ADT versus ADT between the treatment groups for the outcome "overall survival". This resulted in proof of an added benefit of abiraterone-P-ADT in comparison with ADT for this outcome.

This concurs with the assessment of the company, which also derived proof of added benefit.

Morbidity

Symptomatic local disease progression

The outcome "symptomatic local disease progression" was only recorded in the LATITUDE study. There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Skeletal-related events

The meta-analysis showed considerable heterogeneity between the studies for the outcome "skeletal-related events" so that no pooled effect estimate was calculated (see Figure 3 in Appendix A of the full dossier assessment). A statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT was shown in both studies. As described in Section 2.3.1, in case of decisive heterogeneity of the results, the LATITUDE study was used primarily for conclusions on benefit. Due to the high risk of bias for this outcome in the LATITUDE study, only a hint could be derived initially. Since the effect estimates in both studies pointed in the same direction, however, and, in addition, the risk of bias for this outcome was low in the STAMPEDE study, the certainty of conclusions was upgraded to an indication. Overall, there is an indication of an added benefit of abiraterone-P-ADT in comparison with ADT for this outcome.

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

Symptoms (EORTC QLQ-C30 and PR25)

The STAMPEDE study recorded the outcome "symptoms" with the questionnaires EORTC QLQ-C30 and PR25, but results were reported neither for the total population nor for the M1 patient population of the study. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

This concurs with the evaluation of the company, which did not further address the fact that the data were recorded, but not reported, in its assessment.

Health status (EQ-5D VAS)

A statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT was shown for the LATITUDE study for both response criteria considered (deterioration by ≥ 7 and by ≥ 10 points). The extent of this effect in this non-serious/non-severe outcome was overall no more than marginal, however.

The STAMPEDE study recorded the outcome "health status" with the EQ-5D VAS, but results were reported neither for the total population nor for the M1 patient population of the study.

Overall, there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Pain

The LATITUDE study showed a statistically significant difference in favour of abiraterone-P-ADT in comparison with ADT for the outcome "pain", analysed using worst pain (BPI-SF Item 3). This resulted in a hint of an added benefit of abiraterone-P-ADT in comparison with ADT for worst pain (BPI-SF Item 3).

This deviates from the assessment of the company, which derived an indication of an added benefit based on the results for worst pain and average pain intensity.

The STAMPEDE study recorded the outcome "pain" with the EORTC QLQ-C30 pain symptom scale, but results were reported neither for the total population nor for the M1 patient population of the study.

Pain interference

The LATITUDE study showed a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT for pain interference (BPI-SF Items 9 a–g). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. This resulted in no hint of

an added benefit of abiraterone-P-ADT in comparison with ADT for the outcome "pain interference" (BPI-SF Items 9 a–g); an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit based on the results for pain interference.

Fatigue

The LATITUDE study showed a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT for the outcome "fatigue", analysed using worst fatigue (BFI Item 3). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT for worst fatigue; an added benefit is therefore not proven.

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

The STAMPEDE study recorded the outcome "fatigue" with the EORTC QLQ-C30 fatigue symptom scale, but results were reported neither for the total population nor for the M1 patient population of the study.

Fatigue interference

The LATITUDE study showed a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT for the outcome "fatigue interference" (BFI Items 4 a–f). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the clinical irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT for the outcome "fatigue interference"; an added benefit is therefore not proven.

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

Health-related quality of life

Recorded with FACT-P in the LATITUDE study

For the outcome "health-related quality of life", measured in the LATITUDE study with the FACT-P questionnaire, a statistically significant effect in favour of abiraterone-P-ADT in comparison with ADT was shown in the FACT-P total score. This resulted in a hint of an added benefit of abiraterone-P-ADT in comparison with ADT.

This deviates from the assessment of the company, which derived an indication of an added benefit based on the FACT-P total score and based on the analyses of the subscales prostate cancer subscale (PCS) and physical well-being (PWB), as well as the pain-related subscale (PRS) and the Trial Outcome Index (TOI).

Recorded with the EORTC QLQ-C30 in the STAMPEDE study

The STAMPEDE study recorded the outcome "health-related quality of life" with the EORTC QLQ-C30 questionnaire, but results were reported neither for the total population nor for the M1 patient population of the study. Hence there was no hint of an added benefit of abiraterone-P-ADT in comparison with ADT; an added benefit is therefore not proven.

This concurs with the evaluation of the company, which did not further address the fact that the data were recorded, but not reported, in its assessment.

Side effects

For the STAMPEDE study, there were no systematic analyses for AEs for the relevant M1 patient population. Hence greater or lesser harm can only be derived based on the analyses of the LATITUDE study.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from abiraterone-P-ADT in comparison with ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe adverse events (CTCAE grade 3–4)

The LATITUDE study showed a statistically significant difference to the disadvantage of abiraterone-P-ADT in comparison with ADT for the outcome "severe AEs (CTCAE grade 3–4)". This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

This concurs with the company's assessment.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from abiraterone-P-ADT in comparison with ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Fluid retention/oedema

There was no statistically significant difference between the treatment groups for the outcome "fluid retention/oedema". This resulted in no hint of greater or lesser harm from abiraterone-P-ADT in comparison with ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Cardiac failure

There were no usable analyses for the outcome "cardiac failure". This resulted in no hint of greater or lesser harm from abiraterone-P-ADT in comparison with ADT; greater or lesser harm is therefore not proven.

The company did not consider this outcome in its analyses.

Ischaemic heart disease

There were no usable data for the outcome "ischaemic heart disease". This resulted in no hint of greater or lesser harm from abiraterone-P-ADT in comparison with ADT; greater or lesser harm is therefore not proven.

The company did not consider this outcome in its analyses.

Hypokalaemia (CTCAE grade 3–4)

A statistically significant effect to the disadvantage of abiraterone-P-ADT in comparison with ADT was shown for the outcome "hypokalaemia (CTCAE grade 3–4)". This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

The company did not consider this outcome for the derivation of the added benefit.

Alanine aminotransferase increased (CTCAE grade 3–4)

A statistically significant effect to the disadvantage of abiraterone-P-ADT in comparison with ADT was shown for the outcome "alanine aminotransferase (ALT) increased (CTCAE grade 3–4)". This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

The company did not consider this outcome for the derivation of the added benefit.

Aspartate aminotransferase increased (CTCAE grade 3–4)

A statistically significant effect to the disadvantage of abiraterone-P-ADT in comparison with ADT was shown for the outcome "aspartate aminotransferase (AST) increased (CTCAE grade 3–4)". This resulted in a hint of greater harm from abiraterone-P-ADT in comparison with ADT.

The company did not consider this outcome for the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

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

- age (< 65 years versus ≥ 65 or < 70 years versus ≥ 70 years)
- presence of visceral metastasis (yes versus no)
- Gleason score in the primary tumour (< 8 versus ≥ 8)

- number of bone metastases (≤ 10 versus> 10)
- region (East EU, West EU, Asia-Pacific, rest of the world)

From the chosen potential effect modifiers, only subgroup analyses for the characteristics "age" and "Gleason score", and these only for the outcome "overall survival", were available for the STAMPEDE study.

Two different threshold values were used for the subgroup characteristic "age" because different threshold values had been prespecified in the 2 studies (LATITUDE: < 65 versus ≥ 65 years; STAMPEDE: < 70 versus ≥ 70 years).

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

In accordance with the methods described above, there was no relevant effect modification for the present benefit assessment for the outcomes and the operationalizations included.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1]. The approach for deriving an overall conclusion on 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 data presented in Section 2.4 resulted in proof/hints or indications of an added benefit or of greater harm.

Determination of the outcome category for the outcomes on morbidity

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

Health status (EQ-5D VAS)

Recording of the outcome "health status" with the EQ-5D VAS is on a scale of 0 to 100, where the patients assess their health status. A score of 0 indicates the worst and a score of 100 the best imaginable health status.

Patients in the LATITUDE study rated their health status with 74 points at the start of the study. In the course of the study, there was no important deterioration of the average health status; the mean value of the self-assessed health status after 11 cycles was 80 points in the intervention

group and 76 points in the comparator group. Hence the health status experienced by the patients remained in the upper third of the scale and even improved somewhat over the study duration. It could not be inferred from the dossier that the outcome "health status" (EQ-5D VAS) was a serious/severe symptom. The outcome was therefore allocated to the category "non-serious/non-severe".

Worst pain (BPI-SF Item 3)

The information provided on the worst pain experienced by the patients (BPI-SF Item 3) showed that about 50% of the patients indicated a score of 0 to 1 at the start of the study (LATITUDE study). This means that half of the patients either experienced no pain or slight pain as the worst pain. For another 22% of the patients, mild pain was the worst pain experienced. In the course of the study, there was no important deterioration of the worst pain experienced (mean change from the start of the study: −0.30 points [improvement] in the abiraterone arm; +0.15 points in the comparator arm). The outcome was therefore categorized as "non-serious/non-severe symptom".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT

Outcome category **Outcome**	**Abiraterone-P-ADT vs. ADT[a]** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	NA vs. 34.7 – 48 HR 0.62 [0.53; 0.71] p < 0.001 probability: "proof"	Outcome category: "mortality" CI_u < 0.85 added benefit, extent: "major"
Morbidity		
Symptomatic local disease progression	NA vs. NA HR 0.67 [0.42; 1.08] p = 0.101	Lesser benefit/added benefit not proven
Skeletal-related events[d]	NA vs. NA heterogeneous results; there was a statistically significant effect in favour of abiraterone in both studies probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Symptoms (recorded with the EORTC QLQ-C30 and PR25)[e]	Recorded, but not reported	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)		
LATITUDE: time to worsening, response criterion 7 points	9.2 vs. 5.6 HR: 0.81 [0.70; 0.94][f] p = 0.004	Lesser benefit/added benefit not proven
LATITUDE: time to worsening, response criterion 10 points	12.9 vs. 8.3 HR: 0.83 [0.72; 0.97][f] p = 0.015	
STAMPEDE	Recorded, but not reported	
Pain		
Worst Pain (BPI-SF Item 3), time to deterioration, response criterion 2 points	NA vs. NA HR 0.63 [0.52; 0.77] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.8 added benefit, extent: "considerable"
EORTC QLQ-C30 pain symptom scale	Recorded, but not reported	Lesser benefit/added benefit not proven
Pain interference (BPI-SF Items 9 a–g)	−0.14 vs. 0.19[g] MD −0.34 [−0.49; −0.18] p < 0.001 Hedges' g: −0.25 [−0.36; −0.13][h]	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT (continued)

Outcome category **Outcome**	**Abiraterone-P-ADT vs. ADT[a]** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Fatigue		
Worst fatigue (BFI Item 3)	−0.25 vs. 0.09[g] MD −0.34 [−0.52; −0.15] p < 0.001 Hedges' g: −0.21 [−0.33; −0.09][h]	Lesser benefit/added benefit not proven
EORTC QLQ-C30 fatigue symptom scale	Recorded, but not reported	Lesser benefit/added benefit not proven
Fatigue interference (BFI Items 4 a–f)	−0.12 vs. 0.16[g] MD −0.28 [−0.43; −0.12] p < 0.001 Hedges' g: −0.21 [−0.33; −0.09][h]	Lesser benefit/added benefit not proven
Health-related quality of life		
Recorded with FACT-P, total score, time to deterioration, response criterion 10 points	12.9 vs. 8.3 HR 0.85 [0.74; 0.99]; p = 0.035 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Recorded with EORTC QLQ-C30[i]	Recorded, but not reported	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR 0.85 [0.68; 1.07]; p = 0.169	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	13.9 vs. 20.2 HR 1.26 [1.08; 1.48]; HR: 0.79 [0.68; 0.93][j]; p = 0.003 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Discontinuation due to adverse events	12.2% vs. 10.1% RR 1.21 [0.88; 1.66]; p = 0.272	Greater/lesser harm not proven
Specific AEs		
Fluid retention/ oedema	NA vs. NA HR 0.96 [0.69; 1.33]; p = 0.783	Greater/lesser harm not proven
Cardiac failure	No usable data	Greater/lesser harm not proven

(continued)

Table 17: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT (continued)

Outcome category **Outcome**	**Abiraterone-P-ADT vs. ADT[a]** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Ischaemic heart disease	No usable data	Greater/lesser harm not proven
Hypokalaemia (CTCAE grade 3–4)	NA vs. NA HR 6.32 [3.02; 13.21]; HR: 0.16 [0.08; 0.33][j]; $p < 0.001$ probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Alanine aminotransferase (ALT) increased (CTCAE grade 3–4)	NA vs. NA HR 3.99 [1.84; 8.65]; HR: 0.25 [0.12; 0.54][j]; $p < 0.001$ probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Aspartate aminotransferase (AST) increased (CTCAE grade 3–4)	NA vs. NA HR 2.72 [1.27; 5.80]; HR: 0.37 [0.17; 0.79][j]; $p = 0.010$ probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

(continued)

Table 17: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT (continued)

a: LATITUDE study: ADT + placebo for abiraterone and prednisone; STAMPEDE study: ADT.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: No common effect estimate can be provided due to heterogeneous data.
e: The EORTC QLQ-C30 contains 8 relevant morbidity outcomes, 4 of which are symptom scales. The 2 symptom scales of pain and fatigue are grouped separately under the category of pain and fatigue. In addition to the EORTC QLQ-C30, the additional module QLQ-PR25, which contains 4 further prostate cancer-specific symptom scales and 2 functional scales, was recorded in the STAMPEDE study.
f: The extent of the effect in this non-serious/non-severe outcome is no more than marginal.
g: Mean changes per treatment arm in the included study.
h: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
i: The outcome category health-related quality of life of the EORTC QLQ-C30 contains 5 functional scales and one scale on global health status.
j: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MD: mean difference; NA: not achieved; ND: no data;
P: prednisone/prednisolone; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 18: Positive and negative effects from the assessment of abiraterone-P-ADT in comparison with ADT

Positive effects	**Negative effects**
Mortality ▪ overall survival: proof of an added benefit – extent: "major"	–
Serious/severe symptoms/late complications ▪ skeletal-related events: indication of an added benefit – extent: "non-quantifiable"	–
Non-serious/non-severe symptoms/late complications ▪ pain: hint of an added benefit – extent "considerable"	–
Health-related quality of life ▪ recorded with FACT-P: hint of a minor added benefit	–
–	Serious/severe side effects ▪ severe AEs (CTCAE grade 3 –4): hint of greater harm – extent: "minor" ▪ hypokalaemia (CTCAE grade 3–4): hint of greater harm – extent: "major" ▪ alanine aminotransferase (ALT) increased (CTCAE grade 3 –4): hint of greater harm – extent: "major" ▪ aspartate aminotransferase (AST) increased (CTCAE grade 3–4): hint of greater harm – extent "considerable"
Further uncertainties: ▪ For the LATITUDE study, there are no usable data on the specific AEs "cardiac failure" and "ischaemic heart disease". ▪ In the STAMPEDE study, the patient questionnaires EORTC QLQ-C30 and PR25, as well as EQ-5D-5L, were recorded, but the results were reported neither for the total population nor for the M1 patient population. Hence there were incomplete data on the outcome categories of morbidity and health-related quality of life. In addition, there were no systematic analyses on AEs for the M1 patient population of the STAMPEDE study.	
ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACT-P: Functional Assessment of Cancer Therapy-Prostate; P: prednisone/prednisolone	

In the overall consideration, there is proof, an indication and hints of positive effects of abiraterone in the outcome categories of mortality, morbidity and health-related quality of life, as well as hints of negative effects in the outcome category of side effects.

The positive effects with the extents "minor", "considerable" and "major" are accompanied by negative effects with the same extent. There were no usable results for 2 outcomes regarding harm.

For the STAMPEDE study, there were no results for several outcomes that were recorded, but not reported. It cannot be assumed, however, that these would have a decisive negative influence on the overall result.

Overall, there is proof of considerable added benefit of abiraterone-P-ADT in comparison with ADT in patients with newly diagnosed high risk mHSPC.

The result of the assessment of the added benefit of abiraterone in comparison with the ACT is summarized in Table 19.

Table 19: Abiraterone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC)	▪ conventional androgen deprivation therapy (ADT)[b] ▪ if applicable, in combination with a non-steroidal anti-androgen (flutamide or bicalutamide)	Proof of considerable added benefit[c]

a: Presentation of the respective ACT specified by the G-BA.
b: Surgical castration or medical castration using treatment with LH-RH analogues or GnRH antagonists.
c: Patients with brain metastasis or an ECOG/WHO Performance Status of > 2 were not investigated in the studies LATITUDE and STAMPEDE.

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

The assessment described above deviates from that of the company, which derived proof of major added benefit.

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

2.6 List of included studies

LATITUDE

Chi KN, Protheroe A, Rodriguez-Antolin A, Facchini G, Suttman H, Matsubara N et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018; 19(2): 194-206.

Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; 377(4): 352-360.

Janssen Research & Development. A study of abiraterone acetate plus low-dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed participants with high-risk, metastatic hormone-naive prostate cancer (mHNPC): study details [online]. In: ClinicalTrials.gov. 21.12.2017 [Accessed: 11.01.2018]. URL: https://ClinicalTrials.gov/show/NCT01715285.

Janssen Research & Development. A randomized, double-blind, comparative study of abiraterone acetate plus low-dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed subjects with high-risk, metastatic hormone-naive prostate cancer (mHNPC): study 212082PCR3011; clinical protocol [unpublished]. 2012.

Janssen Research & Development. A randomized, double-blind, comparative study of ZYTIGA (abiraterone acetate) plus low-dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed subjects with high-risk, metastatic hormone-naive prostate cancer (mHNPC): study 212082PCR3011; statistical analysis plan [unpublished]. 2016.

Janssen Research & Development. A randomized, double-blind, comparative study of abiraterone acetate plus low dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed subjects with high risk, metastatic hormone-naive prostate cancer (mHNPC): study 212082PCR3011; clinical study report (interim 1) [unpublished]. 2017.

Janssen Research & Development. A randomized, double-blind, comparative study of abiraterone acetate plus low-dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed subjects with high-risk, metastatic hormone-naive prostate cancer (mHNPC): LATITUDE; analyses for German dossier; final datacut [unpublished]. 2017.

Janssen-Cilag International. A randomized, double-blind, comparative study of abiraterone acetate plus low-dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed subjects with high-risk, metastatic hormone-naive prostate cancer (mHNPC) [online]. In: EU Clinical Trials Register. [Accessed: 11.01.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-002940-26.

STAMPEDE

James ND, De Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017; 377(4): 338-351.

Medical Research Council. STAMPEDE: Systemic therapy in advancing or metastatic prostate cancer; evaluation of drug efficacy; a multi-stage multi-arm randomised controlled trial (STAMPEDE); study details [online]. In: ClinicalTrials.gov. 25.09.2017 [Accessed: 11.01.2018]. URL: https://ClinicalTrials.gov/show/NCT00268476.

Medical Research Council. Systemic therapy in advanced or metastatic prostate cancer: evaluation of drug efficacy [online]. In: ISRCTN Registry. 01.08.2017 [Accessed: 11.01.2018]. URL: http://isrctn.com/ISRCTN78818544.

Medical Research Council. STAMPEDE: systemic therapy in advancing or metastatic prostate cancer; evaluation of drug efficacy; a multi-arm multi-stage randomised controlled trial; protocol; version 8.0 [online]. 02.09.2011 [Accessed: 19.02.2018]. URL: http://www.stampedetrial.org/media/1079/mrcctu-stampede-protocol-v80_superseded.pdf.

Medical Research Council. STAMPEDE: systemic therapy in advancing or metastatic prostate cancer; evaluation of drug efficacy; a multi-arm multi-stage randomised controlled trial; protocol; version 15.0 [online]. 29.03.2016 [Accessed: 19.02.2018]. URL: http://www.stampedetrial.org/media/1086/stampede_protocol_v150_clean_superseded.pdf.

Medical Research Council. STAMPEDE: appendices; version 14.0 [online]. 29.03.2016 [Accessed: 19.02.2018]. URL: http://www.stampedetrial.org/media/1118/stampede_appendices_v140_clean_superseded.pdf.

Medical Research Council. STAMPEDE: systemic therapy in advancing or metastatic prostate cancer; evaluation of drug efficacy; a multi-arm multi-stage randomised controlled trial; statistical analysis plan; version 2 [unpublished] [online].

Rydzewska LHM, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. Eur J Cancer 2017; 84: 88-101.

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Janssen-Cilag International. Abirateronacetat (ZYTIGA 500 mg Filmtabletten). 11.2017.

4. MRC Clinical Trials Unit. STAMPEDE [online]. URL: http://www.stampedetrial.org.

5. James ND, De Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017; 377(4): 338-351.

6. Rydzewska LHM, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. Eur J Cancer 2017; 84: 88-101.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-64-abiraterone-acetate-prostate-cancer-benefit-assessment-according-to-35a-social-code-book-v.8672.html.