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Enzalutamide (prostate cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Enzalutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher
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

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Selver Altin
- Christiane Balg
- Klaus Gossens
- Tatjana Hermanns
- Katharina Hirsch
- Florina Kerekes
- Min Ripoll
- Volker Vervölgyi

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BPI-SF	Brief Pain Inventory – Short Form
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life – 5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy – Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MFS	metastasis-free survival
nmCRPC	non-metastatic castration-resistant prostate cancer
PSA	prostate-specific antigen
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	system organ class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug enzalutamide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 May 2020.

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

For the drug to be assessed, the company submitted a dossier for early benefit assessment for the first time as per 19 November 2018. With its decision dated 16 May 2019, the G-BA limited the decision's validity period to 15 May 2020. This expiry was justified by the PROSPER study being ongoing at the time of the initial assessment and by further results on the outcome category of mortality (overall survival) from an interim analysis as well as results from the final analysis being expected in the future.

Research question

The aim of the present report is to assess the added benefit of enzalutamide in comparison with the appropriate comparator therapy (ACT) of a watchful waiting approach while maintaining the existing conventional androgen deprivation therapy (ADT) in patients with high-risk non-metastatic castration-resistant prostate cancer (high-risk nmCRPC).

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment for enzalutamide

Therapeutic indication	**ACT[a]**
Adult men with high-risk non-metastatic, castration-resistant prostate cancer	Watchful waiting approach while maintaining the existing conventional ADT[b]
a. Presented is the ACT specified by the G-BA. b. In the present therapeutic indication, conventional ADT is understood to mean surgical castration or drug-based castration using GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone	

The company followed the G-BA's specification of the ACT.

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

Results

The PROSPER study was included for assessing any added benefit of enzalutamide in patients with high-risk nmCRPC.

Study design

The PROSPER study is a randomized, double-blind, multicentre study comparing enzalutamide in combination with ADT versus treatment with ADT (and additional placebo).

The study included adult men with asymptomatic high-risk nmCRPC. A total of 1401 patients were randomly allocated to either treatment with enzalutamide + ADT or placebo + ADT at a 2:1 ratio. Enzalutamide treatment was administered in accordance with the Summary of Product Characteristics (SPC). Patients had to continue ADT in addition to their study drug. ADT was either drug-based castration using a gonadotropin-releasing hormone (GnRH) agonist/ antagonist or previous bilateral orchiectomy.

Patients were treated until radiographic disease progression (defined as metastasis to the bone and/or soft tissue), initiation of cytotoxic chemotherapy, use of androgen receptor inhibitors or other investigational substances, or treatment discontinuation as decided by the investigator or patient.

The primary outcome of the PROSPER study was metastasis-free survival (MFS); patient-relevant secondary outcomes were overall survival, pain, health status, health-related quality of life, and adverse events.

Following the 1st data cut-off, the PROSPER study was unblinded on 8 September 2017, and an open-label enzalutamide extension phase was initiated in which the patients of the comparator arm (following another screening) were allowed to receive enzalutamide upon the investigator's discretion, while maintaining the existing ADT. The treatment switch was available only to patients who had adhered to the protocol in the double-blind study phase and had not received any other prostate cancer treatment after unblinding. A total of 87 patients (18.6%) switched to enzalutamide treatment while maintaining the existing ADT. However, it remains unclear to what extent the patients of the PROSPER comparator arm who switched to enzalutamide treatment met the conditions for subsequent enzalutamide treatment. Treatment with enzalutamide + ADT was continued until radiographic disease progression or, if the investigator deemed it to be of clinical benefit, beyond said progression.

Patients of either study arm who had failed to qualify or elected not to participate in the open-label enzalutamide extension phase discontinued treatment with the study drug and proceeded to follow-up observation.

For the final 3rd data cut-off, new study results on patient-relevant outcomes are available exclusively for the categories of mortality and adverse events (AEs). For the outcomes of morbidity and health-related quality of life, the company does not present any analyses of the 3rd data cut-off. For these two outcome categories, the results of the 1st data cut-off (28 June 2017) from the initial assessment of enzalutamide (dossier assessment A18-80) are sufficiently informative and are therefore used in the present benefit assessment.

Risk of bias

The risk of bias at study level was rated as low. The risk of bias at the outcome level was rated as high for all patient-relevant outcomes.

Results

Mortality

Overall survival

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

Morbidity

Worst pain (Brief Pain Inventory – Short Form [BPI-SF]; item 3)

The outcome of worst pain was analysed using the BPI-SF questionnaire (item 3). No statistically significant difference between treatment arms was found for time to first deterioration. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

Interference due to pain (BPI-SF; items 9a–g)

The outcome of interference due to pain was surveyed by means of the BPI-SF questionnaire (items 9a-g). No statistically significant difference between treatment arms was found for this outcome. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

Health status (Visual Analogue Scale of the European Quality of Life – 5 Dimensions [EQ-5D])

The outcome of health status was measured using the EQ-5D visual analogue scale. No statistically significant difference between treatment arms was found for this outcome. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

Health-related quality of life

The outcome of health-related quality of life was surveyed using the Functional Assessment of Cancer Therapy – Prostate (FACT-P). No statistically significant difference between treatment arms was found for time to first deterioration. Consequently, there is no hint of added benefit

of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

AEs

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

No statistically significant difference between treatment arms was found for any of the outcomes of SAEs, severe AEs (CTCAE ≥ grade 3), or discontinuation due to AEs. Consequently, none of these outcomes result in a hint of greater or lesser harm from enzalutamide + ADT in comparison with the watchful waiting approach + ADT; greater or lesser harm is therefore not proven.

Renal and urinary disorders

For the outcome of renal and urinary disorders (system organ class [SOC], severe AEs CTCAE grade ≥ 3), a statistically significant difference was found in favour of enzalutamide + ADT. This results in a hint of lesser harm of enzalutamide + ADT in comparison with a watchful waiting approach + ADT. Overall, however, it is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the disease symptoms.

Psychiatric disorders, general disorders and administration site conditions, nervous system disorders, hypertension

For each of the outcomes of psychiatric disorders (SOC, AEs), general disorders and administration site conditions (SOC, severe AEs CTCAE grade ≥ 3), nervous system disorders (SOC, severe AEs CTCAE grade ≥ 3), and hypertension (standardized MedDRA query [SMQ], CTCAE grade ≥ 3), a statistically significant difference was found to the disadvantage of enzalutamide + ADT. This results in a hint of greater harm of enzalutamide + ADT in comparison with a watchful waiting approach + ADT.

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

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

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

Overall, both favourable and unfavourable effects were found for enzalutamide + ADT in comparison with a watchful waiting approach + ADT.

On the favourable side, a hint of considerable added benefit was found for the outcome of overall survival. Further, a favourable effect of enzalutamide was found for the specific AE of renal and urinary disorders (SOC, severe AEs of CTCAE grade ≥ 3), resulting in a hint of lesser harm of considerable extent. However, on the basis of the available information, it remains questionable whether this favourable effect of enzalutamide is in fact attributable to the outcome category of adverse events or rather reflects the progression of the underlying disease.

Regarding unfavourable effects, in contrast, hints of greater harm, some of minor and some of considerable extent, were found for 3 serious/severe specific AEs (general disorders and administration side conditions, nervous system disorders, hypertension). For the non-serious/ non-severe specific AE of psychiatric disorders, there is a hint of greater harm of considerable extent.

Overall, the unfavourable effects on AEs do not offset the favourable effects, particularly regarding overall survival.

In summary, for patients with high-risk non-metastatic castration resistant prostate cancer, there is a hint of considerable added benefit of enzalutamide + ADT versus the ACT of a watchful waiting approach while maintaining conventional ADT (placebo + ADT).

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

Table 3: Enzalutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with high-risk non-metastatic, castration-resistant prostate cancer	Watchful waiting approach while maintaining the existing conventional ADT[b]	Hint of considerable added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. In the present therapeutic indication, conventional ADT is understood to mean surgical castration or drug-based castration using GnRH agonists or GnRH antagonists.
c. Only patients with an ECOG-PS of 0 or 1 were included in the PROSPER study. It remains unclear whether the observed effects also apply to patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone

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

2.2 Research question

The aim of the present report is to assess the added benefit of enzalutamide in comparison with the ACT of a watchful waiting approach while maintaining the existing conventional androgen deprivation therapy (ADT) in patients with high-risk nmCRPC.

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

Table 4: Research questions of the benefit assessment of enzalutamide

Therapeutic indication	**ACT[a]**
Adult men with high-risk non-metastatic castration-resistant prostate cancer	Watchful waiting approach while maintaining the existing conventional ADT[b]
a. Presented is the ACT specified by the G-BA. b. In the present therapeutic indication, conventional ADT is understood to mean surgical castration or drug-based castration using GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone	

The company followed the G-BA's specification of the ACT.

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

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on enzalutamide (as of 16 March 2020)
- Bibliographic literature search on enzalutamide (most recent search on 16 March 2020)
- Search in trial registries / study results databases on enzalutamide (most recent search on 16 March 2020)
- Search on the G-BA website on enzalutamide (most recent search on 16 March 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on enzalutamide (most recent search on 20 May 2020)

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

Table 5: Study pool – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT

Study	Study category			Available sources		
	Approval study for the drug to be assessed (Yes/No)	Sponsored study[a] (Yes/No)	Third-party study (Yes/No)	Clinical study report (Yes/No [reference])	Registry entries[b] (Yes/No [reference])	Publication and other sources (Yes/No [reference])
MDV3100-14 (PROSPER[c])	Yes	Yes	No	No[d]	Yes [3-8]	Yes [9-12][e]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this short name.
d. Due to working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data provided in Module 5 of the company's dossier.
e. The publication [10] is not cited in Module 4 A since it was published after the dossier's submission date.

ADT: Androgen deprivation therapy; RCT: randomized controlled trial

2.3.2 Study characteristics

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

Table 6: Characterization of the included study – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
PROSPER	RCT, double-blind, unblinded after the 1st data cut-off[b]; parallel group	Adult men with high-risk non-metastatic castration-resistant prostate cancer[c]	Enzalutamide + ADT (N = 933) Placebo + ADT (N = 468)	**Double-blind phase** Screening: starting 28 days before randomization Treatment: until disease progression (or continuing after progression as long as the patient was deemed by the investigator to benefit from the treatment), initiation of cytotoxic chemotherapy, use of androgen receptor inhibitors, or investigational substances, or treatment discontinuation as decided by the investigator or the patient. **Open-label enzalutamide extension phase[d]** Treatment: until disease progression or continuing after progression, provided that in the investigator's opinion, there was an additional clinical benefit of enzalutamide Follow-up observation of both study phases[e]: outcome-specific, at the longest until death, discontinuation of study participation, or study end	254 study centres in Argentina, Austria, Australia, Belgium, Brazil, Canada, Chile, China, Denmark, Finland, France, Germany, Greece, Hong Kong, Italy, Korea, Malaysia, Netherlands, New Zealand, Poland, Russia, Sweden, Serbia, Singapore, Slovakia, Spain, Taiwan, Thailand, Turkey, United Kingdom, Ukraine, USA 11/2013–10/2019 1st data cut-off: 28/06/2017 2nd data cut-off: 31/05/2018 3rd data cut-off: 15/10/2019	Primary: metastasis-free survival Secondary: overall survival, pain, health status, health-related quality of life, AEs

Table 6: Characterization of the included study – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Data on secondary outcomes were included only concerning available outcomes relevant for this benefit assessment. b. After the target criterion for the primary outcome of metastasis-free survival was reached, the PROSPER study was unblinded (8 September 2017). The study was then continued without blinding (enzalutamide extension phase, long-term follow-up phase). c. The patient inclusion criteria specified a testosterone serum value ≤ 50 ng/dL and a PSA value ≥ 2 µg/L at screening as well as 3 PSA rises (at ≥ 1-week intervals between measurements) before study inclusion. The study defined high-risk prostate cancer using a PSA doubling time ≤ 10 months. d. Open-label enzalutamide extension phase: Patients from the intervention arm were allowed to continue treatment with enzalutamide + ADT. Patients from the comparator arm (with or without disease progression) who completed the double-blind phase according to protocol and did not receive any other subsequent treatment for prostate cancer were allowed to switch to treatment with enzalutamide + ADT. Patients who had been deemed by the investigator to be unsuitable for the open-label enzalutamide extension phase or who had chosen not to participate in it discontinued the study drug. e. Outcome-specific information is provided in Table 8. ADT: androgen deprivation therapy; AE: adverse event; N: number of randomized patients; PSA: prostate-specific antigen; RCT: randomized controlled trial						

Table 7: Characterization of the intervention – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT

Study	Intervention	Comparison
PROSPER	**Double-blind phase:**	
	Enzalutamide 160 mg orally once daily (four 40 mg capsules) + ADT[a] Dose interruption or reduction to 120 mg or 80 mg daily allowed in case of the occurrence of AEs	Placebo orally once daily (4 capsules) + ADT[a]
	Open-label enzalutamide extension phase	
	All patients received enzalutamide 160 mg orally once daily (four 40-mg capsules) + ADT[a] Dose interruption or reduction as in the double-blind phase	
	Prior treatment Allowed: ▪ ADT with GnRH agonist or antagonist ▪ Bilateral orchiectomy Disallowed: ▪ Cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for treating prostate cancer ▪ Investigational drug inhibiting androgen synthesis or the androgen receptor ▪ Hormone therapy (e.g. androgen receptor inhibitors, oestrogens, 5-α reductase inhibitors) or biologic therapies for the treatment of prostate cancer or substance in clinical testing (4 weeks before study start) **Concomitant treatment** Allowed: ▪ Double-blind phase: bisphosphonates or denosumab (continued intake of a stable dose defined ≥ 4 weeks before randomization) ▪ Open-label extension phase: The initiation of bisphosphonates or denosumab for bone health was allowed. ▪ Calcium and vitamin D ▪ Drugs for lowering the seizure threshold Disallowed: ▪ Cytotoxic chemotherapy ▪ Androgen receptor inhibitors ▪ Investigational drugs Allowed only in exceptional cases: ▪ CYP3A4 inductor (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) ▪ CYP2C9 inductor (e.g. phenytoin, warfarin) ▪ CYP2C19 inductor (e.g. S-mephenytoin) ▪ Strong or moderate CYP2C8 inhibitors (e.g. rifampin, gemfibrozil[b])	

a. Except for patients with a history of orchiectomy.
b. Administration allowed only in case of enzalutamide dose reduction to 80 mg.

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

Study design

The PROSPER study is a randomized, double-blind, multicentre study comparing enzalutamide in combination with ADT versus treatment with ADT (and additional placebo).

The study included adult men with asymptomatic high-risk nmCRPC. High-risk prostate cancer was defined by a prostate-specific antigen (PSA) doubling time ≤ 10 months. Further, patients had to have a serum testosterone value ≤ 50 ng/dL (≤ 1.73 nmol/L) and a PSA value ≥ 2 µg/L as well as 3 rises in PSA value during ADT (PSA1 < PSA2 < PSA3; at ≥ 1-week intervals between each measurement) before study inclusion.

In the study, a total of 1401 patients were randomly allocated at a 2:1 ratio to either treatment with enzalutamide + ADT or placebo + ADT. Randomization was stratified by PSA doubling time (< 6 months/≥ 6 months) and by the use of bone-targeting agents at study start (yes/no).

In the PROSPER study, enzalutamide treatment was administered in accordance with the SPC (Table 7) [13]. Patients had to continue ADT in addition to their study drug. ADT was either drug-based castration using a GnRH agonist/antagonist or previous bilateral orchiectomy.

A subsequent therapy was received by 34.2% of patients from the intervention arm and 66.2% of patients from the comparator arm of the study. The discrepancy is due to the fact that radiographically determined disease progression occurred much earlier in the comparator arm. There were no restrictions concerning the type of subsequent therapy following the end of treatment. After failure of the combined hormone therapy (enzalutamide + ADT) in the intervention arm, the subsequent therapy most commonly received by these patients was docetaxel (20.2%), followed by abiraterone (16.3%). In the comparator arm, abiraterone was the most common subsequent therapy (38.3%), followed by docetaxel (30.8%) (Appendix C, Table 26 of the full report). The percentage of patients with subsequent therapies was smaller than that of patients with treatment discontinuation (see Table 9). This discrepancy cannot be explained by the occurrence of deaths alone. Thus, it remains unclear what caused the described differences. The primary outcome of the PROSPER study was MFS; patient-relevant secondary outcomes were overall survival, pain, health status, health-related quality of life, and AEs.

Data cut-offs and course of the study

The PROSPER study started on 26 November 2013 and, according to data provided in Module 4 A, was completed on 15 October 2019 (3rd data cut-off). The protocol predefined that the interim analysis with a statistically significant difference between groups in terms of overall survival was to be viewed as the final analysis.

Three preplanned data cut-offs are available:

- 1st data cut-off (on 28 June 2017): planned analysis of the primary outcome of MFS after approximately 440 MFS events; analysis of all further secondary outcomes

- 2nd data cut-off (on 31 May 2018): planned interim analysis for the outcome of overall survival after approximately 285 deaths; analysis of the outcome of overall survival only
- 3nd data cut-off (on 15 October 2019): planned interim analysis for the outcome of overall survival after approximately 440 deaths; analyses on the outcome of overall survival and the outcome category of adverse events; additional analyses on the outcomes of time to start of new antineoplastic therapy or cytotoxic chemotherapy

Double-blind study phase

After randomization, patients were treated until radiographic disease progression (defined as metastasis to the bone and/or soft tissue), initiation of cytotoxic chemotherapy, use of androgen receptor inhibitors or other investigative substances, or treatment discontinuation as decided by the investigator or patient. Under certain conditions, the continued administration of the study drug was allowed even after progression upon the investigator's discretion. About 30 days after the intake of the last study drug or immediately before the initiation of a new antineoplastic therapy (provided this therapy was initiated less than 30 days after the last study drug intake), AEs were surveyed one last time and morbidity and quality of life outcomes measured.

In the subsequent long-term follow-up observation (every 16 weeks), radiographic examinations were continued for patients without proven radiographic disease progression, and the survival status and initiation of a new antineoplastic therapy for prostate cancer was recorded. Morbidity and quality of life outcomes continued to be surveyed in patients whose follow-up visits took place in hospital.

Open-label enzalutamide extension phase (after the 1st data cut-off)

The 1st data cut-off took place after approximately 440 events concerning the primary outcome of MFS (28 June 2017). Following the 1st data cut-off, the PROSPER study was unblinded on 8 September 2017.

With the 4th amendment to the study protocol (26 January 2018), an open-label enzalutamide extension phase was initiated (open-label period), in which (following another screening) patients in the comparator arm were allowed to receive enzalutamide upon the investigator's discretion while maintaining the existing ADT. The treatment switch was available only to patients who had adhered to the protocol in the double-blind study phase (without disease progression or with disease progression but continued study drug) and had not received any other prostate cancer treatment after unblinding. These criteria were met by 114 patients of the comparator arm [10]. From this group, 87 (18.6% of all patients of the comparator arm) switched to treatment with enzalutamide while maintaining the existing ADT (cross-over group).

Treatment with enzalutamide + ADT was continued until radiographic disease progression or beyond that time if the investigator deemed it to be of clinical benefit. Survival status, initiation

of new prostate cancer treatment, AEs, and concomitant drugs were surveyed. Morbidity and quality of life outcomes were not further recorded.

Patients of either study arm who had failed to be included or chosen not to participate in the open-label enzalutamide extension phase discontinued treatment with the study drug and proceeded to follow-up observation.

Comment on the study design

Patients in the placebo + ADT arm were allowed to switch to the enzalutamide arm (while maintaining ADT), provided they had exhibited no disease progression during the double-blind study phase or continued to receive the study drug despite disease progression.

The treatment of patients with non-metastatic castration-resistant prostate cancer fits the research question of the present benefit assessment. The treatment switch from the comparator to the intervention arm therefore might potentially lead to bias in terms of the treatment effect. Module 4 A does not provide any data on the percentage of patients without disease progression who switched to the enzalutamide arm.

Enzalutamide is an approved treatment option for patients with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated [13]. For these patients, the administration of enzalutamide as subsequent therapy should not to be viewed as treatment switching as defined by [14]. However, it remains unclear to what extent patients in the PROSPER comparator arm who switched to the enzalutamide arm after disease progression met the conditions for subsequent enzalutamide treatment.

The resulting uncertainties are taken into account in the assessment of the outcome-specific risk of bias.

Data cut-offs used for the assessment

All patient-relevant outcomes from the relevant PROSPER study were used to derive added benefit, taking into account the 3rd data cut-off.

For the outcomes of morbidity and health-related quality of life, the company does not present any analyses of the 3rd data cut-off. For the present benefit assessment, the data of the 1st data cut-off (28 June 2017) from the initial assessment of enzalutamide (dossier assessment A18-80 [12]) were used. Since a large percentage of the study population already exhibited an event at this data cut-off point, the results from a later PROSPER analysis point are unlikely to differ from it in a material way. Further, the informative value of results from the 3rd data cut-off would be further limited due to selective outcome recording (see Table 8).

This approach differs from that of the company, whose Module 4 A deviates from the limitation specified by the G-BA [15] by presenting only outcomes for which results on the 3rd data cut-off are available (overall survival and AEs). Hence, in deriving added benefit, the company

fails to take into account the results on morbidity (outcomes of worst pain, interference by pain, and health status) and health-related quality of life (see Section 2.5.2).

Implementation of the ACT

The G-BA specified the ACT as a watchful waiting approach while maintaining the existing, conventional ADT. For the present benefit assessment, a watchful waiting approach was operationalized as a follow-up strategy which particularly comprises diagnosis of disease progression.

In the PROSPER study, regular visits were conducted at 16-week intervals. During these visits, patients' disease progression was examined by imaging techniques (magnetic resonance imaging, computed tomography, bone scintigraphy).

In accordance with the current S3 guideline, follow-up should include imaging based on symptoms and potential therapeutic consequences [16]. Routine radiographic examinations – as done in the PROSPER study – are not specified in the guideline. Nonetheless, the study visits were spaced far apart (4 months) and, if disease progression was suspected, radiographic screening was also provided outside of routine visits. The diagnostic procedure of the PROSPER study is therefore considered appropriate.

Follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
PROSPER	
Mortality	
Overall survival	Until death
Morbidity	
Pain (BPI-SF)	Double-blind phase: 30 days after treatment end and thereafter for patients without progression[a] until death[b]; not measured in the open-label extension phase
Health status (EQ-5D VAS)	Double-blind phase: 30 days after treatment end and thereafter for patients without progression[a] until death[b]; not measured in the open-label extension phase
Health-related quality of life (FACT-P)	Double-blind phase: 30 days after treatment end and thereafter for patients without progression[a] until death[b]; not measured in the open-label extension phase
AEs	
All outcomes of the adverse events category	Up to 30 days after treatment end

a. Presented in accordance with information in the study protocol. In the commenting procedure on the initial assessment of enzalutamide [17], the company reported that the outcome was recorded in all patients with a hospital visit, regardless of disease progression.
b. Recorded only for patients whose long-term follow-ups took place in hospital.

ADT: androgen deprivation therapy, AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; EQ-5D: European Quality of Life – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; RCT: randomized controlled trial; VAS: visual analogue scale

The follow-up durations for the outcome categories of morbidity, health-related quality of life, and AE have been systematically shortened since the outcomes were surveyed only for the period of treatment with the study drug (plus 30 days). Patient-relevant morbidity and quality-of-life outcomes were also surveyed in the long-term follow-up observation of the blinded study phase, but only for patients whose long-term follow-ups took place in hospital.

Due to this approach, insufficient information is available on the patients' follow-up care strategy. Effects of subsequent therapies, which are an integral part of the watchful waiting approach (as a consequence of the observation), were insufficiently recorded. Radiographic disease progression occurred earlier in patients in the comparator arm. Hence, it stands to reason that patients in the comparator arm received subsequent therapy much earlier as well, a fact which may influence patient-relevant outcomes. It is unclear to what extent the differences between treatment arms with regard to the conduct of subsequent therapies would also be reflected by the results on AEs, morbidity, and health-related quality of life.

Drawing reliable conclusions covering the entire study period or until patient death would also require that said outcomes be surveyed and analysed – just like overall survival – in all patients for the entire study period.

Characterization of the study population

Table 9 shows the patient characteristics in the included study.

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

Study Characteristic Category	**Enzalutamide + ADT N[a] = 933**	**Placebo + ADT N[a] = 468**
PROSPER		
Age [years], mean (SD)	74 (7.8)	73 (7.6)
Region, n (%)		
North America	141 (15.1)	63 (13.5)
Europe	458 (49.1)	232 (49.6)
Rest of the world	334 (35.8)	173 (37.0)
Gleason Score at diagnosis, n (%)		
2–4	21 (2.3)	12 (2.6)
5–7	491 (52.6)	230 (49.1)
8–10	381 (40.8)	207 (44.2)
Unknown	40 (4.3)	19 (4.1)
ECOG Performance Status at baseline, n (%)		
0	747 (80.1)	382 (81.6)
1	185 (19.8)	85 (18.2)
≥ 2	0 (0)	0 (0)
Missing	1 (0.1)	1 (0.2)
PSA doubling time [months], n (%)		
< 6	715 (76.6)	361 (77.1)
≥ 6	217 (23.3)	107 (22.9)
Missing	1 (0.1)	0 (0)
Time from initial diagnosis / 1st treatment until randomization [months]		
Median [min; max]	90.4 [2.2; 381.8]	86.8 [2.2; 275.7]
Orchiectomy	119 (12.8)	62 (13.2)
Endocrine therapy, n (%)	807 (86.8)	405 (87.1)
Leuprorelin	399 (42.9)	185 (39.8)
Goserelin	253 (27.2)	136 (29.2)
Triptorelin	141 (15.2)	77 (16.6)
Degarelix	53 (5.7)	20 (4.3)
Disease status at baseline		
Not metastatic	910 (98)	454 (97)
Metastatic[b]	23 (2)	14 (3)
Use of bone-targeting agents at baseline, n (%)	105 (11)	48 (10)
Treatment discontinuation, n (%)	552 (59.2)	465 (99.4)[d]
Study discontinuation[c], n (%)		
During the treatment phase	ND	ND
During long-term follow-up observation	367 (39.3)	244 (52.1)[e]

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

Study Characteristic Category	Enzalutamide + ADT Na = 933	Placebo + ADT Na = 468
a. Number of randomized patients (ITT population: all patients who were randomized into one of the two treatment arms, whether or not they actually received the study drug). b. After study inclusion, the presence of metastatic prostate cancer was diagnosed by a blinded, independent radiographic expert. c. Including study discontinuation due to death: 288 (30.9%) in the intervention arm vs. 178 (38.0%) in the comparator arm. d. Including 18.6% of patients from the comparator arm who switched to enzalutamide + ADT after unblinding. e. IQWiG calculations. ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group Performance Status; ITT: intention to treat; max: maximum; min.: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; PSA: prostate specific antigen; RCT: randomized controlled trial; SD: standard deviation		

The demographic and clinical characteristics of patients in the treatment arms of the PROSPER study are broadly comparable. The average age of study participants was 73 years; most participants were from Europe (49%), and the mean time from initial prostate cancer diagnosis to randomization was about 7 years. As ADT, most patients (approx. 87%) received drug-based castration with GnRH agonists or GnRH antagonists. A small percentage (approx. 13%) of study participants had been surgically castrated (orchiectomy). More than 80% of patients had an Eastern Cooperative Oncology Group Performance Status of 0 (fully active, able to carry on all pre-disease performance without restriction).

Duration of treatment and follow-up observation

Table 10 shows the patients' means and medians for both treatment duration and follow-up observations in terms of individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Enzalutamide + ADT** **N = 933**	**Placebo + ADT** **N = 468**
PROSPER		
Treatment duration [a, b, c] [months]		
Median [min; max]	33.9 [0.2; 68.8]	14.2 [0.1; 51.3]
Mean (SD)	33.4 (17.8)	15.8 (10.5)
Observation period [months]		
Overall survival		
Median [min; max]	42.3 [0.7; 69.0]	38.7 [3.7; 69.8]
Mean (SD)	41.4 (14.6)	38.8 (14.9)
Morbidity	ND	
Health-related quality of life	ND	
Adverse events[a, c] – censored[d]		
Median [min; max]	34.5 [0.7; 68.8]	14.7 [0.0; 51.3]
Mean (SD)	33.8 (17.7)	16.4 (10.7)

a. In the enzalutamide + ADT arm, this includes the double-blind phase and the open-label enzalutamide extension phase; in the placebo + ADT arm, it includes only the double-blind phase.
b. Difference between "day of last dose of study drug" and "day of first dose of study drug", divided by 30.4375.
c. Relative to all randomized patients who received at least one (partial) dose of the study drug.
d. Patients with a treatment switch from placebo + ADT to enzalutamide + ADT are censored at the time of the 1st intake of enzalutamide; follow-up observation for patients of the placebo arm without censoring: median [min; max]: 15.6 [0.9; 62.8] months; mean (SD): 19.6 (14.4) months.

ADT: androgen deprivation therapy; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration at the 3rd data cut-off point of the PROSPER study is substantially longer in the intervention arm (3.9 months) than in the comparator arm (14.2 months).

The median follow-up duration for overall survival is 42.3 months in the intervention arm and 38.7 months in the comparator arm.

Data on follow-up duration are lacking with respect to the outcome categories of morbidity and health-related quality of life.

The median follow-up duration for the outcome category of AEs is 34.5 months in the intervention arm and 14.7 months in the comparator arm. Since AEs were recorded up to 30 days after treatment end, a shortened follow-up duration in the comparator arm can be explained by an earlier end of treatment (especially due to earlier radiographically determined disease progression).

Risk of bias across outcomes (study level)

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

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

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

a. The study was unblinded after the 1st data cut-off (28/06/2017).

ADT: androgen deprivation therapy; RCT: randomized controlled trial

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

After reaching the target criterion for the primary outcome of MFS, the PROSPER study was unblinded on 8 September 2017. Restrictions resulting from the open-label study design after the study was unblinded are described in Section 2.4 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

In Module 4 A (Section 4.3.1.2.1), the company states that the extent to which the demographic data and characteristics at the start of the PROSPER study are comparable with the high-risk nmCRPC population in Germany can be assessed only to a limited extent.

The company argues that there is no evidence to suggest that the characteristics of patients in Germany would differ from those of the study population. The company points out that both diagnostic criteria, treatment guidelines, and available treatment options in Germany match those in the countries from which patients were included in the study. According to the company's conclusion, sufficient comparability of the health care context and hence transferability of the study results can be assumed. In this regard, the company reports that a high percentage of recruited patients (49.3% of the study population) came from Europe.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Worst pain (measured using the Brief Pain Inventory – Short Form [BPI-SF]; Item 3)
  - Interference due to pain (measured using the BPI-SF; items 9a–g)
  - Health status (measured with the Visual Analogue Scale [VAS] of the EQ-5D)
- Health-related quality of life
  - Measured using the FACT-P total score
- AEs
  - SAEs
  - Severe AEs (CTCAE Grade ≥ 3)
  - Discontinuation due to AEs
  - Further specific AEs, if any

The selection of patient-relevant outcomes departs from the selection by the company, which uses further outcomes in Module 4 A of the dossier (for the reasoning, see Section 2.7.4.3.2 of the initial assessment A18-80).

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

Table 12: Matrix of outcomes – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT

Study	Outcomes								
	Overall survival	**Worst pain (BPI-SF Item 3)**	**Interference due to pain (BPI-SF; item 9a–g)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (FACT-P)**	**SAEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Discontinuation due to AEs**	**Specific AEs[a]**
PROSPER	Yes	Yes[b]	Yes[b]	Yes[b]	Yes[b]	Yes	Yes	Yes	Yes

a. The following events have been assessed (MedDRA coding): "psychiatric disorders (SOC, AEs)", "general disorders and administration site conditions (SOC, severe AEs)", "nervous system disorders (SOC, severe AEs)", "renal and urinary disorders (SOC, severe AEs)", and "hypertension (SMQ, severe AEs)".

b. The outcome was not further recorded in the open-label enzalutamide extension phase or was generally recorded only selectively during long-term follow-up observation in patients who came to the hospital for the visit. In Module 4 A, the company does not present an analysis of this outcome at the 3rd data cut-off point, and the informative value of results would be questionable due to selective outcome recording. The present benefit assessment uses the data of the 1st data cut-off (28 June 2017) from the initial assessment of enzalutamide (dossier assessment A18-80 [12]) since, at that data cut-off, a large percentage of the study population had already experienced an event. Therefore, the results from a later analysis point of the PROSPER study are unlikely to materially depart from those of the 1st data cut-off.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SOC: system organ class; SAE: serious adverse event; VAS: visual analogue scale

2.4.2 Risk of bias

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

Table 13: Risk of bias at study and outcome levels – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT

Study	Study level	Outcomes								
		Overall survival	Worst pain (BPI-SF item 3)	Interference due to pain (BPI-SF; items 9a–g)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Specific AEs[a]
PROSPER	L	H[b]	H[c, d]	H[d, e]	H[d, e]	H[c, d]	H[d]	H[d]	H[f]	H[d, f]

a. The following events have been assessed (MedDRA coding): "psychiatric disorders (SOC, AEs)", "general disorders and administration site conditions (SOC, severe AEs)", "nervous system disorders (SOC, severe AEs)", "renal and urinary disorders (SOC, severe AEs)", and "hypertension (SMQ, severe AEs)".
b. A total of 18.6% of patients from the comparator arm switched to enzalutamide treatment. It remains unclear what percentage of these treatment switchers were patients without disease progression (off label).
c. More than 10% of randomized patients were excluded from analysis due to missing values.
d. Potentially informative censoring or incomplete observation given different discontinuation behaviours between treatment arms.
e. Unknown percentage of patients excluded from analysis.
f. Lack of blinding with subjective decision on discontinuation (discontinuation due to AEs) or lack of blinding with subjective outcome collection (exclusively for non-serious/non-severe specific AEs and hence the SOC of psychiatric disorders).

ADT: androgen deprivation therapy; AE: adverse event; PI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; H: high; MedDRA: Medical Dictionary for Regulatory Activities; L: low; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SOC: system organ class; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias of the results for the outcome of overall survival is rated as high. This rating results from the fact that, for 18.6% of patients who switched from the placebo + ADT arm to the enzalutamide + ADT arm, it remains unclear whether subsequent therapy with enzalutamide doses should be viewed as treatment switching within the meaning of [14] (see Section 2.3.2; "Comment on study design").

The questionnaire return rates for the survey of morbidity and health-related quality of life exhibit major discrepancies between study arms (see Section 2.7.4.2 of the initial assessment of enzalutamide [12]). These discrepancies can be largely explained by the vast difference between arms in radiographically determined progression events and hence by different follow-up observation periods. While treatment discontinuation did not necessarily end the surveying of morbidity and health-related quality of life, long-term observation was provided only to patients who presented for visits at the hospital even after the end of treatment. Moreover, analyses regarding the outcomes of worst pain (BPI-SF item 3) and health-related quality of

life (FACT-P) included only patients for whom data were recorded at baseline and at one more time point. Hence, > 10% of included patients are missing from the analysis. In terms of interference due to pain (BPI-SF; items 9a–g) and health status (EQ-5D VAS), the percentage of patients missing from the analysis is unclear, but is likely > 10% as well. These aspects result in a high risk of bias of results for the outcomes of worst pain (BPI-SF item 3), interference due to pain (BPI-SF; items 9a–g), health status (EQ-5D VAS), and health-related quality of life (FACT-P).

AEs were measured for the period of treatment with the study drug or at a single time point 30 days after the last intake of the study drug. In the placebo + ADT arm, this includes only the double-blind study phase, whereas in the enzalutamide + ADT arm, it includes the double-blind phase and the open-label enzalutamide extension phase. The above-mentioned discrepancies in observation durations between study arms, mainly due to the study design and differences in progression events between treatment arms, might potentially lead to informative censoring. Therefore, the risk of bias is rated as high for the results of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), and specific AEs.

For the results of the non-serious/non-severe AEs of psychiatric disorders (SOC), the risk of bias is additionally rated as high due to partial lack of blinding (after unblinding on 8 September 2017) with subjective recording of outcomes.

In terms of the results of the outcome of discontinuation due to AEs, the high risk of bias results from the partial lack of blinding with subjective decision on discontinuation.

This assessment departs from that by the company, which rates the results of all included outcomes as having a low risk of bias.

2.4.3 Results

Table 14 and Table 15 summarize the results for the comparison of enzalutamide + ADT with placebo + ADT in patients with high-risk nmCRPC. Where necessary, the data from the company's dossier are complemented by IQWiG calculations.

The results for common AEs, SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs from the 3rd data cut-off (15 October 2019) are presented in Appendix A of the present benefit assessment. Kaplan-Meier curves on the included event-time analyses are shown in Appendix B.

Table 14: Results (mortality, AEs, time to event) – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT (multi-page table)

Study Outcome category Outcome	Enzalutamide + ADT N	Enzalutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Enzalutamide + ADT vs. placebo + ADT HR [95% CI]; p-value[a]
PROSPER					
Mortality (3rd data cut-off)					
Overall survival	933	67.0 [64.0; NR] 288 (30.9)	468	56.3 [54.4; 63.0] 178 (38.0)	0.73 [0.61; 0.88]; 0.001
Morbidity (1st data cut-off)					
Worst pain (BPI-SF item 3)[b, c]	839	18.5 [18.3; 22.1] 390 (41.8)	415	18.5 [14.8; 25.8] 165 (35.3)	0.98 [0.82; 1.18]; 0.838
Health-related quality of life (1st data cut-off)					
FACT-P total score[b, d]	839	11.1 [11.0; 14.7] 499 (53.5)	415	11.1 [11.1; 14.7] 226 (48.3)	0.97 [0.82; 1.14]; 0.700
Physical well-being (PWB) *(presented as supplementary information)*[b, e]	839	7.9 [7.5; 11.1] 538 (57.7)	415	11.5 [11.1; 14.8] 206 (44.0)	-
Social well-being (SWB) *(presented as supplementary information)*[b, e]	839	18.4 [14.8; 22.2] 398 (42.7)	415	14.8 [11.1; 18.6] 187 (40.0)	-
Emotional well-being (EWB) *(presented as supplementary information)*[b, e]	839	25.8 [22.0; 29.4] 359 (38.5)	415	18.4 [14.7; 18.6] 173 (37.0)	-
Functional well-being (FWB) *(presented as supplementary information)*[b, e]	839	11.0 [7.5; 11.1] 534 (57.2)	415	11.1 [10.7; 14.6] 229 (48.9)	-
PCS *(presented as supplementary information)*[b, e]	839	7.8 [7.5; 11.1] 549 (58.8)	415	7.7 [7.4; 11.1] 264 (56.4)	-
AEs (3rd data cut-off)					
AEs[f] *(Presented as supplementary information)*	930	1.0 [0.9; 1.3] 873 (93.9)	465	2.8 [1.9; 3.5] 379 (81.5)	-
SAEs[f]	930	53.6 [47.5; NR] 345 (37.1)	465	NR [NR; NR] 97 (20.9)	0.94 [0.74; 1.19]; 0.610

Table 14: Results (mortality, AEs, time to event) – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT (multi-page table)

Study Outcome category Outcome	Enzalutamide + ADT N	Enzalutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Enzalutamide + ADT vs. placebo + ADT HR [95% CI]; p-value[a]
Severe AEs (CTCAE grade ≥ 3)[f]	930	40.8 [37.3; 46.9] 424 (45.6)	465	40.5 [31.9; NR] 124 (26.7)	1.05 [0.85; 1.29]; 0.637
Discontinuation due to AEs[f]	930	NR [NR; NR] 133 (14.3)	465	NR [NR; NR] 37 (8.0)	1.01 [0.69; 1.48]; 0.946
Specific AEs					
Psychiatric disorders (SOC, AEs)	930	NR [NR; NR] 148 (15.9)	465	NR [NR; NR] 26 (5.6)	2.17 [1.42; 3.31]; < 0.001
General disorders and administration site conditions (SOC, severe AEs)	930	NR [NR; NR] 75 (8.1)	465	NR [NR; NR] 10 (2.2)	2.21 [1.13; 4.32]; 0.018
Nervous system disorders (SOC, severe AEs)	930	NR [NR; NR] 61 (6.6)	465	NR [NR; NR] 8 (1.7)	2.16 [1.02; 4.59]; 0.04
Renal and urinary disorders (SOC, severe AEs):	930	NR [NR; NR] 81 (8.7)	465	NR [NR; NR]; 46 (9.9)	0.43 [0.29; 0.63]; < 0.001
Hypertension (SMQ[g], severe AEs)	930	NR [NR; NR] 54 (5.8)	465	NR [NR; NR] 11 (2.4)	1.99 [1.03; 3.82]; 0.036

a. Effect and CI: Cox PH model; p-value: Log rank test. Both stratified by PSA doubling time and use of bone-targeting agents.
b. The analysis includes only patients for whom values were recorded at baseline and at least one other time point.
c. Time to first deterioration by ≥ 2 points.
d. Time to first deterioration by ≥ 10 points.
e. Time to first deterioration by ≥ 3 points.
f. Without events classified as progression of the underlying disease.
g. Based on the information from Module 4 A, the SMQ of hypertension presumably comprises PTs of severity CTCAE ≥ 3.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: Hazard Ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PCS: prostate-cancer specific subscale of FACT-P; PH: proportional hazards; PSA: prostate-specific antigen; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: system organ class

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

Study Outcome category Outcome	Enzalutamide + ADT			Placebo + ADT			Enzalutamide + ADT vs. placebo + ADT
	N[a]	Values at baseline mean (SE)	Change by Week 97 Mean[b] (SE)	N[a]	Values at baseline mean (SE)	Change by Week 97 Mean[b] (SE)	MD [95% CI]; p-value[b]
PROSPER							
Morbidity (1st data cut-off)							
Pain intensity (BPI-SF items 3–6) *(presented as supplementary information)*[c]	839	ND	0.49 (0.1)	415	ND	0.55 (0.16)	−0.06 [−0.40; 0.29] ND
Interference due to pain (BPI-SF 9a–g)[c]	839	ND	0.65 (0.1)	415	ND	0.85 (0.16)	−0.20 [−0.53; 0.13]; ND
Health status (EQ-5D VAS)[d]	836	ND	−4.57 (0.91)	414	ND	−5.29 (1.47)	0.72 [−2.30; 3.75]; 0.639

a. Number of patients for whom at least a value at baseline and another recorded value is available.
b. Mean per arm, effect, CI, and p-value: mixed effect model repeated measurement (MMRM)
c. A positive change from baseline to study end means deterioration, a negative effect estimator means an advantage of the intervention.
d. A negative change from baseline to study end means deterioration; a positive effect estimator means an advantage of the intervention.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; EQ-5D: European Quality of Life – 5 Dimensions; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SE: standard error; VAS: visual analogue scale

Due to the high risk of bias, at most hints, e.g. of an added benefit, can be derived on the basis of the available data for all examined outcomes.

Mortality

Overall survival

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

This assessment deviates from that by the company, which derives an indication of added benefit for the outcome of overall survival.

Morbidity

Worst pain (BPI-SF item 3)

The outcome of worst pain was analysed using the BPI-SF questionnaire (item 3). No statistically significant difference between treatment arms was found for time to first deterioration. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

This departs from the company's approach in that the company's dossier disregards the outcome of worst pain.

Interference due to pain (BPI-SF; items 9a–g)

The outcome of interference due to pain was surveyed by means of the BPI-SF questionnaire (items 9a-g). No statistically significant difference between treatment arms was found for this outcome. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

This departs from the company's approach in that the company's dossier disregards the outcome of interference due to pain.

Health status (EQ-5D VAS)

The outcome of health status was measured using the EQ-5D visual analogue scale. No statistically significant difference between treatment arms was found for this outcome. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

This departs from the company's approach in that the company's dossier disregards the outcome of health status.

Health-related quality of life (FACT-P)

The outcome of health-related quality of life was surveyed using the FACT-P. No statistically significant difference between treatment arms was found for time to first deterioration. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the watchful waiting approach + ADT; an added benefit is therefore not proven.

This departs from the company's approach in that the company's dossier disregards the outcome of health-related quality of life.

AEs

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

No statistically significant difference between treatment arms was found for any of the outcomes of SAEs, severe AEs (CTCAE ≥ grade 3), and discontinuation due to AEs. Consequently, none of these outcomes result in a hint of greater or lesser harm from enzalutamide +

ADT in comparison with the watchful waiting approach + ADT; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

Renal and urinary disorders

For the outcome of renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3), a statistically significant difference was found in favour of enzalutamide + ADT. This results in a hint of lesser harm of enzalutamide + ADT in comparison with a watchful waiting approach + ADT. Overall, however, it is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the disease symptoms.

This departs from the assessment by the company, which derives an indication of lesser harm for the outcome of renal and urinary disorders.

Psychiatric disorders, general disorders and administration site conditions, nervous system disorders, hypertension

For each of the outcomes of psychiatric disorders (SOC, AEs), general disorders and administration site conditions (SOC, severe AEs CTCAE grade ≥ 3), nervous system disorders (SOC, severe AEs CTCAE grade ≥ 3), and hypertension (Standardized MedDRA Query [SMQ], CTCAE grade ≥ 3), a statistically significant difference was found to the disadvantage of enzalutamide + ADT. This results in a hint of greater harm of enzalutamide + ADT in comparison with a watchful waiting approach + ADT.

This departs from the assessment by the company, which derives an indication of greater harm for all outcomes. For the outcome of hypertension, the company used the results of the PT (CTCAE grade ≥ 3) rather than those of the SMQ.

2.4.4 Subgroups and other effect modifiers

The subgroup characteristic of age (< 75 years/≥ 75 years) is relevant for the present assessment.

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

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

Subgroup analyses are available for all included patient-relevant outcomes (except for the outcome of health status).

When applying the above-described methods, the available subgroup results show no effect modifications.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of added benefit at outcome level

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

Determination of the outcome category for outcomes on AEs

Not for all outcomes considered in the present benefit assessment does the dossier specify whether they were serious/severe or non-serious/non-severe. The categorization method used for these outcomes is explained below.

Specific AEs

The specific AE of psychiatric disorders (SOC) is categorized as non-serious/non-severe since the events associated with this outcome were predominantly non-serious/non-severe.

The specific AEs of general disorders and administration site conditions (SOC), nervous system disorders (SOC), renal and urinary disorders (SOC), and hypertension (SMQ) are categorized as serious/severe since events associated with these outcomes have a CTCAE grade ≥ 3.

Table 16: Extent of added benefit at outcome level: enzalutamide + ADT vs. watchful waiting approach + ADT (multi-page table)

Outcome category **Outcome**	**Enzalutamide + ADT vs. placebo + ADT** **Median time to event (months) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	67.0 vs. 56.3 HR: 0.73 [0.61; 0.88]; p = 0.001 Probability: hint	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit, extent: considerable
Morbidity		
Worst pain (BPI-SF item 3)	18.5 vs. 18.5 HR: 0.98 [0.82; 1.18]; p = 0.838	Lesser/added benefit not proven
Interference due to pain (BPI-SF; items 9a–g)	Mean: 0.65 vs. 0.85 MD: −0.20 [−0.53; 0.13]; p = ND	Lesser/added benefit not proven
Health status (EQ-5D VAS)	Mean: −4.57 vs. −5.29 MD: 0.72 [−2.30; 3.75]; p = 0.639	Lesser/added benefit not proven
Health-related quality of life		
FACT-P total score	11.1 vs. 11.1 HR: 0.97 [0.82; 1.14]; p = 0.700	Lesser/added benefit not proven
AEs		
SAEs[c]	53.6 vs. NR HR: 0.94 [0.74; 1.19]; p = 0.610	Greater/lesser harm not proven
Severe AEs[c] (CTCAE grade ≥ 3)	40.8 vs. 40.5 HR: 1.05 [0.85; 1.29]; p = 0.637	Greater/lesser harm not proven
Discontinuation due to AEs[c]	NR vs. NR HR: 1.01 [0.69; 1.48]; p = 0.946	Greater/lesser harm not proven
Psychiatric disorders (SOC, AEs)	NR vs. NR HR: 2.17 [1.42; 3.31]; HR: 0.46 [0.3; 0.7][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable

Table 16: Extent of added benefit at outcome level: enzalutamide + ADT vs. watchful waiting approach + ADT (multi-page table)

Outcome category **Outcome**	**Enzalutamide + ADT vs. placebo + ADT** **Median time to event (months) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
General disorders and administration site conditions (SOC, severe AEs)	NR vs. NR HR: 2.21 [1.13; 4.32]; HR: 0.45 [0.23; 0.88][d]; p = 0.018 Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Nervous system disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 2.16 [1.02; 4.59]; HR: 0.46 [0.22; 0.98][d]; p = 0.04 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)	NA vs. NA HR: 0.43 [0.29; 0.63]; p < 0.001 Probability: hint	Outcome category: serious/severe AEs[e] $CI_u < 0.75$, risk ≥ 5% Lesser harm; extent: considerable
Hypertension (SMQ, severe AEs [CTCAE grade ≥ 3])	NR vs. NR HR: 1.99 [1.03; 3.82]; HR: 0.5 [0.26; 0.97][d]; p = 0.036 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u).
c. Without events classified as progression of the underlying disease.
d. IQWiG calculation, reversed direction of effect to enable the use of limits for deriving the extent of added benefit.
e. It is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the symptoms of the disease.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: Hazard Ratio; MD: mean difference; NR: not reached; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: system organ class; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

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

Table 17: Favourable and unfavourable effects from the assessment of enzalutamide + ADT versus a watchful waiting approach + ADT

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival: hint of added benefit – extent: considerable	–
Serious/severe AEs[a] ▪ Renal and urinary disorders (severe AEs CTCAE grade ≥ 3): hint of lesser harm – extent: considerable	Serious/severe AEs ▪ General disorders and administration site conditions (severe AEs CTCAE grade ≥ 3): hint of greater harm – extent: considerable ▪ Nervous system disorders (severe AEs CTCAE grade ≥ 3): hint of greater harm – extent: minor ▪ Hypertension (severe AEs CTCAE grade ≥ 3): hint of greater harm – extent: minor
–	Non-serious/non-severe AEs ▪ Psychiatric disorders (AEs): hint of greater harm – extent: considerable
a. It is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the symptoms of the disease. ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

Overall, both favourable and unfavourable effects were found for enzalutamide + ADT in comparison with a watchful waiting approach + ADT.

On the favourable side, a hint of considerable added benefit was found for the outcome of overall survival. Further, a favourable effect of enzalutamide was found for the specific AE of renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3), resulting in a hint of lesser harm of considerable extent. However, on the basis of the available information, it remains questionable whether this favourable effect of enzalutamide is in fact attributable to the outcome category of AEs or rather reflects the symptoms of the underlying disease.

Regarding unfavourable effects, in contrast, hints of greater harm, some of minor and some of considerable extent, were found for 3 serious/severe specific AEs (general disorders and administration side conditions, nervous system disorders, hypertension). For the non-serious/ non-severe specific AE of psychiatric disorders, there is a hint of greater harm of considerable extent.

Overall, the unfavourable effects on AEs do not offset the favourable effects, particularly regarding overall survival.

In summary, for patients with high-risk non-metastatic castration resistant prostate cancer, there is a hint of considerable added benefit of enzalutamide + ADT versus the ACT of a watchful waiting approach while maintaining conventional ADT (placebo + ADT).

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

Table 18: Enzalutamide – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult men with high-risk non-metastatic castration-resistant prostate cancer	Watchful waiting approach while maintaining the existing conventional ADT[b]	Hint of considerable added benefit[c]
a. Presented is the ACT specified by the G-BA. b. In the present therapeutic indication, conventional ADT is understood to mean surgical castration or drug-based castration using GnRH agonists or GnRH antagonists. c. Only patients with an ECOG-PS of 0 or 1 were included in the PROSPER study. It remains unclear whether the observed effects apply to patients with an ECOG-PS ≥ 2. ADT: androgen deprivation therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone		

The above assessment deviates from that by the company, which derived an indication of considerable added benefit.

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

Supplementary information on the implementation of the conditions of the limitation

In the justification paper of the first decision on enzalutamide, the G-BA specified the following conditions of the limitation:

> *"In 2020, the ongoing PROSPER study will be releasing an interim analysis for all outcomes after 440 deaths. A new benefit assessment after expiry of the time limit will require these findings to be included in its dossier." [15]*

In its dossier, the company only partially meets these requirements. The company derives an added benefit of enzalutamide exclusively on the basis of the results of the 3rd data cut-off of the PROSPER study. For this data cut-off, no analyses of the results on patient-relevant outcomes in the morbidity and health-related quality of life categories are available. It should be noted that the design of the PROSPER study generally does not lend itself to fully capturing any effects of subsequent therapies, which are an integral component of the watchful waiting approach. In Module 4 A, the company does not present results from the 1st data cut-off on patient-relevant outcomes of the categories of morbidity and health-related quality of life. Hence, the company fails to consider the entirety of the evidence for deriving an added benefit of enzalutamide.

References for English extract

Please see full dossier assessment for full reference list.

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

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