20 September 2018
EMA/41918/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xtandi

International non-proprietary name: enzalutamide

Procedure No. EMEA/H/C/002639/II/0039/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADT	androgen deprivation therapy
ADR	adverse drug reaction
APTC	Antiplatelet Trialists' Collaboration
AR	androgen receptor
ASCO	American Society of Clinical Oncology
BICR	blinded independent central review
CRPC	castration-resistant prostate cancer
CT	computed tomography
CYP	cytochrome P450
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels health questionnaire
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FAS	full analysis set
HR	hazard ratio
ISS	Integrated Summary of Safety
ITT	intent-to-treat
M0	Non metastatic
MACE	major cardiovascular events
MFS	metastasis-free survival
MI	myocardial infarction
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OS	overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PFS	progression-free survival
PRES	posterior reversible encephalopathy syndrome
PSA	prostate-specific antigen
PSA-P	prostate-specific antigen progression
QoL	quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
rPFS	radiographic progression-free survival
SCS	Summary of Clinical Safety
SMQ	standardized MedDRA query
TEAE	treatment-emergent adverse event
Tg	Transgenic
WH	Wistar Hannover

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 29 January 2018 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.4: Update of sections 4.4, 4.7, 4.8 and 5.2 of the SmPC in order to amend the warning on possible association with seizure, to amend the effects on driving or operating machines, to amend the identified adverse reactions and to amend the 'Race' subsection regarding pharmacokinetic properties based on the results from the completed studies PROSPER, a Phase 3 Randomized Controlled Study, designed to investigate the Safety and Efficacy of Enzalutamide in Patients with Non-Metastatic Castration-Resistant Prostate Cancer; and Asian PREVAIL, a Multinational Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Oral Enzalutamide in Chemotherapy-naive Subjects with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy; and the updated integrated clinical safety database.
The Package Leaflet is updated in accordance.

C.I.6.a: Extension of Indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC) for Xtandi;
as a consequence, sections 4.1 and 5.1 of the SmPC are updated, based on the supportive clinical study results of MDV3100-14 (PROSPER), a Phase 3 Randomized Controlled Study, designed to investigate the Safety and Efficacy of Enzalutamide in Patients with Non-Metastatic Castration-Resistant Prostate Cancer; MDV3100-09 (STRIVE), a Multicenter Phase 2 Study to investigate the Safety and Efficacy of Enzalutamide Versus Bicalutamide in Men With Non-Mtastatic or Metastatic Castration-Resistant Prostate Cancer; and based on supportive non-clinical data from 7 new reports.
The Package Leaflet is updated in accordance.

An update RMP version 12.5 was submitted in order to include the changes related to the extension of indication.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

Scientific Advice was given from CHMP/SAWP on the 17th of January 2013, pertaining to the non-clinical and clinical development (EMEA/H/SA/1612/1/FU/2/2012/III).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	29 January 2018
Start of procedure:	3 March 2018
CHMP Co-Rapporteur Assessment Report	30 April 2018
CHMP Rapporteur Assessment Report	7 May 2018
PRAC Rapporteur Assessment Report	4 May 2018
PRAC Outcome	17 May 2018
CHMP members comments	24 May 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 May 2018
Request for supplementary information (RSI)	31 May 2018
PRAC Rapporteur Assessment Report	4 July 2018
CHMP Rapporteur Assessment Report	12 July 2018
PRAC Outcome	12 July 2018
CHMP members comments	19 July 2018
Updated CHMP Rapporteur Assessment Report	20 July 2018
Request for supplementary information (RSI)	26 July 2018
PRAC Rapporteur Assessment Report	28 August 2018
CHMP Rapporteur Assessment Report	7 September 2018
PRAC Outcome	6 September 2018

Timetable	Actual dates
SAG meeting	6 September 2018
CHMP members comments	12 September 2018
Updated CHMP Rapporteur Assessment Report	14 September 2018
Opinion	20 September 2018

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

This application is for extending the indication of enzalutamide to include treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease (PSA doubling time ≤ 10 months and PSA levels ≥ 2 ng/mL).

Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses despite castrate levels of testosterone while on treatment with a luteinizing-hormone releasing hormone analogue (LHRHa), or following bilateral orchiectomy. This disease was previously known as hormone-refractory prostate cancer until research demonstrated that the majority of these resistant cancers overexpress the AR and may remain sensitive to more potent hormonal agents than those approved at the time (e,g., first generation antiandrogens such as flutamide or bicalutamide) [Chen et al, 2004].

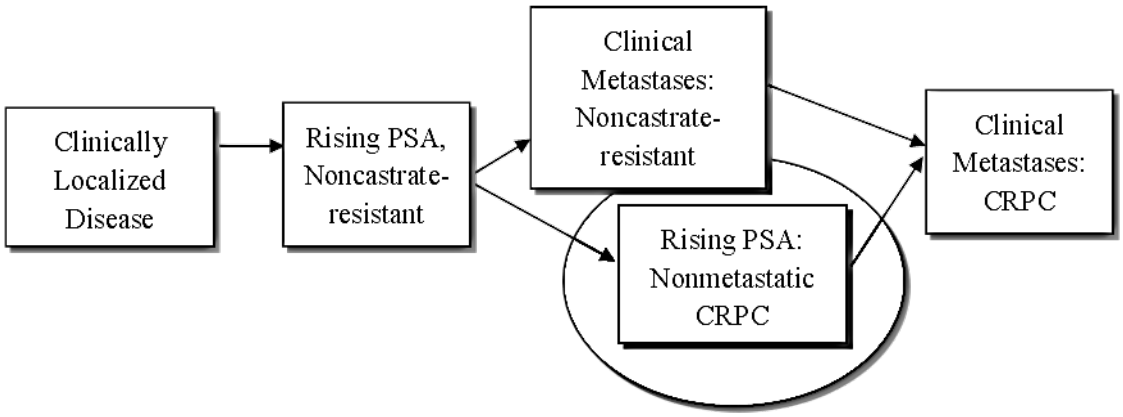
2.1.2. Epidemiology

In Europe (France, Germany, Italy, Spain, United Kingdom), it is estimated that NM-CRPC represents 7% of all prostate cancer cases. The current prediction is that the 5-year prevalence will increase in the future from 89,810 patients in 2016 to 110,290 patients in 2026.

In the United States (US), the incidence of NM-CRPC has been estimated to be 50,000 to 60,000 men per year, with a 34% annual rate of progression to metastatic CRPC (mCRPC), with rapidly rising PSA [ie, a PSA doubling time (PSADT) of ≤ 10 months] conferring greater risk. Of NM-CRPC patients, 33% developed bone metastasis within 2 years.

2.1.4. Clinical presentation, diagnosis and stage

Prostate cancer progresses through a series of characteristic clinical states that represent both the natural history of the disease and the response to treatment, as depicted in the below figure [Scher & Heller, 2000].



Following the initial evaluation and diagnosis of prostate cancer, approximately 90% of men undergo primary localized treatment with curative intent [Cooperberg et al, 2010]. Androgen deprivation therapy (ADT) (i.e., surgical or medical castration) is often initiated in men with rising prostate-specific antigen (PSA) after primary therapy. Following ADT, the next most frequent clinical state in the current model of prostate cancer progression is that of CRPC, defined as disease progression despite castrate hormone levels (testosterone ≤ 50 ng/dL).

Men with CRPC can have metastatic or non-metastatic disease, which has traditionally been determined by means of computed tomography (CT) or magnetic resonance imaging (MRI), as well as radionuclide bone scans. In the majority of patients, metastatic CRPC evolves from non-metastatic CRPC and PSA doubling time has been shown to be a strong predictor of the development of metastases in these patients. Thus, PSA doubling time is reported as a useful prognostic factor in identifying patients at high-risk of development of clinically detectable metastatic disease (i.e., disease progression) [Moreira et al, 2015; Scher et al, 2015]. Various studies have assessed a range of PSA doubling times, with one study showing that a PSA doubling time of < 6 months was associated with an 11-fold higher risk of disease progression compared with a PSA doubling time of > 10 months [Nguyen et al, 2015].

2.1.5. Management

No therapy is currently approved for, nor has shown delay in, progression from non-metastatic to metastatic CRPC.

Although high-risk non-metastatic CRPC (i.e., for patients with a short PSA doubling time) is a disease state, current treatment options are limited. Per a provisional opinion from the American Society of Clinical Oncology (ASCO), second-line hormonal therapy (e.g., antiandrogens, cytochrome P450 [CYP] 17 inhibitors) may be considered in patients with nonmetastatic CRPC at high risk for metastatic disease (based on a short PSA doubling time or rapid velocity), but otherwise this treatment is not suggested [Virgo et al, 2017]. Similarly, the National Comprehensive Cancer Network (NCCN) guideline recommends first-generation antiandrogens (e.g., bicalutamide, nilutamide, flutamide), second-generation novel hormonal therapies (enzalutamide, abiraterone), ketoconazole, corticosteroids or diethylstilbestrol as second-line hormonal therapies [NCCN, 2017]. The European Society for Medical Oncology guidelines advise ADT and watchful waiting [Parker et al, 2015]. Thus, although continued use of ADT is part of clinical practice, no therapy is approved specifically for the treatment of patients with nonmetastatic CRPC.

About the product

Enzalutamide (MDV3100) is a potent oral AR inhibitor that targets the androgen receptor (AR) signaling pathway. Enzalutamide competitively inhibits androgen binding to the AR and, consequently, inhibits nuclear translocation of the AR and inhibits the association of the AR with DNA even in the setting of AR overexpression and in prostate cancer cells resistant to anti androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity.

Enzalutamide is currently approved for the treatment of adult men with metastatic castration-resistant prostate cancer (CRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated; and for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

Type of Application and aspects on development

This application seeks to broaden the current enzalutamide indication to include patients with non-metastatic CRPC.

The initially proposed wording was “the treatment of adult men with non-metastatic castration-resistant prostate cancer”.

The finally approved wording was “the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer”.

Xtandi is available in two pharmaceutical forms; capsule and tablet. The recommended dose is 160 mg enzalutamide as a single oral daily dose. This extension of indication covers both forms.

2.2. Non-clinical aspects

2.2.1. Introduction

Nonclinical data for enzalutamide were previously included in the original marketing authorisation and variations to the marketing authorisation. Additional nonclinical studies have been submitted to support the current marketing application:

- An *in vitro* plasma protein binding in nontransgenic littermate of transgenic rasH2 (non-Tg rasH2) mice and Wistar Hannover (WH) rats (Study 9785-ME-0045) submitted to support the calculation of free exposure.
- A carcinogenicity program was completed to support the approval of enzalutamide at an earlier stage in the prostate cancer disease process.
    - A 26-week carcinogenicity study in Tg rasH2 mice (Study 9785-TX-0020).
    - A 2-year carcinogenicity study in WH rats (Study 9785-TX-0017).

2.2.2. Pharmacology

No additional nonclinical pharmacology studies were submitted to support the current application (see non-clinical discussion).

2.2.3. Pharmacokinetics

Nonclinical pharmacokinetic data for enzalutamide (MDV3100), metabolite MDPC0001, a carboxylic acid derivative (M1) and metabolite MDPC0002, desmethyl-enzalutamide (M2) were included in the original marketing application and in the subsequent variation application related the chemotherapy-naïve indication.

In the original marketing application, the *in vitro* plasma protein binding of enzalutamide, M1 and M2 was determined by equilibrium dialysis in plasma from mouse (CD1 [ICR]), rat (Sprague Dawley), rabbit, monkey and/or human.

An additional study was performed with 14C-enzalutamide, 14C-M1 and 14C-M2 in order to determine the plasma protein binding of enzalutamide, M1 and M2 in non-transgenic littermate of transgenic rasH2 (non-Tg rasH2) mouse and Wistar Hanover (WH) rat plasma by equilibrium dialysis [Study 9785-ME-0045]; the same mouse and rat strains used in the enzalutamide carcinogenicity studies.

Plasma protein binding ratio of 14C-enzalutamide in non-Tg rasH2 mouse and WH rats ranged from 96.8% to 97.7% and 95.0% to 95.9%, respectively. Respective plasma protein binding ratio of 14C-M1 ranged from 92.6% to 92.9% and 96.5% to 96.9%. Respective plasma protein binding ratio of 14C-M2 ranged from 93.8% to 94.0% and 91.0% to 91.5%.

The in vitro plasma protein binding of enzalutamide was generally comparable in mouse (95% to 98%), rat (94% to 96%), rabbit (88% to 90%), dog (94% to 96%) and human (97% to 98%) [Study PRO3100NC32 and Study 9785-ME-0045 combined]. The extent of binding was constant over a wide range of concentrations, 0.05 to 25 µg/mL for all species (0.5 to 25 µg/mL for female rabbits, non-Tg rasH2 mouse and WH rat plasma).

Table 1: *In Vitro* Plasma Protein Binding of [^{14}C]MDV3100, [^{14}C]MDPC0001, and [^{14}C]MDPC0002 in Non-Tg rasH2 Mice and Wistar Han Rats

Study Number	[9785-ME-0045]			
Species	Mouse/Non-Tg rasH2 Rat/Wistar Hanover			
Gender (M/F)/Number of Animals	M/3†			
Method of Administration	In vitro			
Test System	Equilibrium dialysis			
Radionuclide	^{14}C-enzalutamide, ^{14}C-M1, ^{14}C-M2			
Specific Activity (MBq/mg)	^{14}C-enzalutamide (4.68), ^{14}C-M1 (4.84), ^{14}C-M2 (4.79)			
Analyte/Assay	Radioactivity / liquid scintillation counting			
Species (Strain)	**Concentration (µg/mL)**	**Protein binding ratio (%)**		
		Enzalutamide	**M1**	**M2**
Mouse (Non-Tg rasH2)	0.5	97.7 ± 0.1	92.7 ± 0.2	93.9 ± 0.6
	2.5	97.2 ± 0.2	92.9 ± 0.1	94.0 ± 0.5
	25	96.8 ± 0.6	92.6 ± 0.1	93.8 ± 0.3
Rat (Wistar Hanover)	0.5	95.4 ± 0.3	96.8 ± 0.0	91.5 ± 0.3
	2.5	95.9 ± 0.3	96.9 ± 0.1	91.3 ± 0.4
	25	95.0 ± 0.1	96.5 ± 0.0	91.0 ± 0.7
Additional Information: None				

2.2.4. Toxicology

Carcinogenicity

Study 9785-TX-0020

Study 9785-TX-0020 is a 26-week definitive carcinogenicity study in Tg rasH2 mice (both sexes).

In the preliminary 4-week DRF study in non-Tg rasH2 mice [Study 9785-TX-0019], enzalutamide related mortality at doses of 30 and 60 mg/kg per day occurred within the first week of dosing. There was no additional mortality at ≥ 30 mg/kg per day during the remaining 3 weeks of the study. Decreased spontaneous movement, bradypnea and/or hypothermia were observed prior to mortality or when moribund animals were sacrificed. However, the cause of mortality or moribundity could not be established. Based on the findings in the DRF study, 20 mg/kg per day was used as the highest dose in Study 9785-TX-0020 in Tg rasH2 mice. The low (2 mg/kg/day) and mid (6 mg/kg/day) doses were selected to cover a wide range of clinical exposure margins and study dose response.

Enzalutamide was administered by daily oral gavage to male and female Jic:CB6F1-Tg rasH2@Jcl mice (26 or 30 animals/sex per group, 8 weeks of age at the start of dosing) for 26 weeks, at dose levels of 0 (negative control, water for injection), 0 (vehicle control, Labrasol), 2, 6 and 20 mg/kg per day as solution in Labrasol; dosing volume 10 mL/kg. Sixteen animals of each sex were included for the positive control group (N-methyl-N-nitrosourea [MNU] 75 mg/kg, intraperitoneal, once). Systemic exposure (plasma concentrations) of enzalutamide and its metabolites (M1 and M2) was determined in satellite animals (non-Tg rasH2 mice) on day 1 and during week 26 of the dosing period, and toxicokinetic analysis was completed.

At 20 mg/kg per day, there was mortality of 2 males on days 3 and 4, respectively, of the dosing period. A potential cause for the mortality during the first few days of dosing could be lower food consumption, likely due to the unpalatable effect of Labrasol. Similar mortalities were also observed during the first 4 days of the dosing period in the 4-week DRF study in non Tg rasH2 mice [Study 9785-TX-0019]. In the DRF study, there was a transient body weight decrease (first 4 days of dosing) and reduced food consumption in all groups but mortalities only occurred at doses ≥ 30 mg/kg per day up to day 7 of the dosing period. To account for possible early mortalities in the definitive 26 week study in Tg rasH2 mice, 30 mice per sex were initially assigned to the 20 mg/kg per day high dose group. Following 2 weeks of dosing, 2 additional males (plus 2 mortalities) and 4 females were excluded from the 20 mg/kg per day dose group and the number of animals were adjusted to 26 mice per sex (similar to the other dose groups). There was no additional mortality or adverse clinical signs during the remaining period of the study (24 weeks). In the positive control group (MNU), there was mortality of all males and 11 of 16 females during the study duration, mainly due to neoplastic findings. The neoplastic findings are summarized in the table below.

Table 2: Neoplastic findings (all animals) [Study 9785-TX-0020]

Sex	Male					Female				
Dose (mg/kg/day)	0†	0‡	2	6	20	0†	0‡	2	6	20
No. of animals used	26	26	26	26	26	26	26	26	26	26
No. of deaths	3	3	3	3	2	1	2	3	5	2
Thymus										
Thymoma, benign	0	0	1	1	0	0	1	0	1	0
Spleen										
Hemangiosarcoma	3	4	2	2	2	1	1	1	0	0
Lung										
Adenoma, bronchiolo-alveolar	0	1	2	3	0	1	1	1	1	1
Carcinoma, bronchiolo-alveolar	0	1	0	0	0	0	0	1	0	0
Stomach										
Papilloma, squamous cell	2	1	0	2	0	0	2	1	0	0
Carcinoma, squamous cell	0	0	0	0	0	0	0	0	1	0
Liver										
Adenoma, hepatocellular	2	0	0	0	0	0	0	0	0	0
Harderian gland										
Adenoma	2	0	2	0	0	0	0	0	0	1
Adenocarcinoma	0	1	0	0	0	0	0	0	0	0
Hemolymphoreticular (all sites)										
Lymphoma, malignant	1	0	0	0	0	1	0	0	0	0
All sites of blood vessel tumor§										
Hemangioma and Hemangiosarcoma	4	4	3	5	4	3	2	3	0	3

† Negative control group (water for injection)

‡ Vehicle control group (Labrasol)

§ Tumors in abdominal cavity, sternum, spleen, stomach, kidney, testis, uterus, vagina, skin/subcutis, ear, hind limb and clitoral gland were included.

Number in the table indicates the number of animals with respective lesions.

Source: [Study 9785-TX-0020]

Apart from the 2 initial mortalities, there were no enzalutamide-related clinical findings, visible palpable masses, body weight or food consumption changes in any dose group. All neoplastic findings were considered spontaneous, related to age and background.

Histopathology revealed no enzalutamide-related neoplastic findings in either sex [table below]. In the positive control group, the Tg rasH2 mice demonstrated high sensitivity to MNU-induced neoplastic findings, which included a high incidence of malignant lymphoma and papilloma/carcinoma of the squamous cells in the forestomach.

The non-neoplastic findings are summarized in the table below.

Table 3: Summary of Test Article-related Nonneoplastic Lesions

Sex	Male					Female				
Dose (mg/kg/day)	0†	0‡	2	6	20	0†	0‡	2	6	20
No. of animals used	26	26	26	26	26	26	26	26	26	26
No. of deaths	3	3	3	3	2	1	2	3	5	2
Gallbladder	[25]	[26]	[25]	[25]	[26]	[25]	[25]	[25]	[23]	[24]
Hyalinosis (Total)	0	0	0	4	7	0	7	9	11	8
(±)	0	0	0	4	4	0	5	6	4	1
(+)	0	0	0	0	3	0	2	3	7	7
Testis	[26]	[26]	[26]	[26]	[26]	NA	NA	NA	NA	NA
Vacuolation, decreased, Leydig cell (±)	0	0	0	6	26					
Seminal vesicle	[26]	[26]	[26]	[26]	[26]	NA	NA	NA	NA	NA
Atrophy (+)	0	1	0	1	11					
Adrenal	[26]	[26]	[26]	[26]	[26]	[26]	[26]	[26]	[26]	[26]
Eosinophilic change, zona fasciculata (total)	0	0	0	0	25	0	0	0	0	23
(±)	0	0	0	0	22	0	0	0	0	22
(+)	0	0	0	0	3	0	0	0	0	1

[ ]: Number of animals examined; ±: Minimal, +: Mild, ++: Moderate, +++: Severe; NA: Not applicable.
† Negative control group (water for injection)
‡Vehicle control group (Labrasol)

Enzalutamide-related non-neoplastic findings (compared to vehicle) in both sexes included minimal to mild increase in hyalinosis of the gallbladder at doses ≥ 6 mg/kg per day (adversity unknown) and minimal to mild eosinophilic change adrenal zona fasciculata at a dose of 20 mg/kg per day (nonadverse). Although the hyalinosis was observed at low incidence in the Labrasol control group and at 2 mg/kg per day in females (indicative of a vehicle related change), the severity and incidence of the finding was exacerbated at ≥ 6 mg/kg per day in both sexes. There were no degenerative changes in gallbladder epithelium associated with the hyalinosis finding. At ≥ 6 mg/kg per day, findings in males only included minimal decrease in vacuolation of the Leydig cells in the testes (nonadverse) and at 20 mg/kg per day, additional findings in males included small size of prostate (without microscopic correlate) and small size seminal vesicle with correlated mild atrophy (nonadverse). Enzalutamide-related changes in the adrenal, testes, seminal vesicle and/or prostate were observed in previously reported toxicity studies in mice [Study 9785 TX 0019], rats [Studies PRO3100NC17; 9785 TX-0016] and dogs [Study 9785-TX-0010], and are consistent with its pharmacological activity (inhibition of the AR signaling).

Other than hyalinosis in the gallbladder, Labrasol-related findings (compared to water control) included inflammation and/or regeneration in the bronchus and trachea, erosion/ulcer, inflammation and hyperplasia of the squamous cells in the forestomach corresponding to macroscopic lesions, hypertrophy in the centrilobular hepatocytes in the liver and minimal to mild hemorrhage in the Rathke's cleft in the pituitary.

Study 9785-TX-0017

In this 2 year carcinogenicity study in rats (dose levels: 0, 10, 30 and 100 mg/kg per day), increased incidences of the following tumours were considered treatment-related in male Wistar Han (WH) rats: Leydig cell tumour in the testis (≥ 10 mg/kg per day); benign thymoma in the thymus (≥ 10 mg/kg per day); and urothelial papilloma/carcinoma in the urinary bladder, adenoma of pars distalis in the pituitary and fibroadenoma in the mammary gland (100 mg/kg per day). In female WH rats, treatment-related increases in adenoma of pars distalis in the pituitary (≥ 30 mg/kg per day) and benign granulosa cell tumour in the ovary (100 mg/kg per day) were noted.

Toxicokinetic data

Following oral administration, exposure (Cmax and AUC24h) of enzalutamide (parent) and its metabolites (M1 and M2) increased with increasing dose; there was no sex difference in exposure and accumulation was observed (parent and metabolites) following repeat administration for 26 weeks [Study 9785-TX-0020]. The exposure (Cmax and AUC24h) for enzalutamide was higher than those of the metabolites (M1 and M2); the exposures of M1 and M2 were similar. The tmax for enzalutamide ranged from 4 to 12 hours, and the tmax for metabolites ranged from 4 to 12 hours (see Table below).

Table 4: Toxicokinetic Parameters (Week 26) for Enzalutamide, M1 and M2 Following Oral Administration of Enzalutamide to Non-Tg rasH2 Mice [Study 9785-TX-0020]

Analyte	Dose† (mg/kg)	Sex (M/F)	C_{max} (µg/mL)	t_{max} (h)	AUC_{24h} (µg·h/mL)	Metabolite Ratio to Enzalutamide‡ (%)	Accumulation Index§
Enzalutamide	2	M	2.29	8	37.5	NA	1.57
		F	2.06	12	40.1	NA	1.59
	6	M	5.94	8	110	NA	1.63
		F	6.83	4	121	NA	1.46
	20	M	15.7	4	286	NA	1.23
		F	18.0	8	348	NA	1.26
M1	2	M	0.320	4	5.77	15	8.15
		F	0.173	8	3.00	7	3.41
	6	M	0.547	4	8.76	8	3.38
		F	0.533	4	7.96	7	2.41
	20	M	1.21	4	18.8	7	1.90
		F	1.82	8	25.0	7	2.26
M2	2	M	0.0990	4	1.90	5	4.64
		F	0.0839	12	1.64	4	2.36
	6	M	0.368	8	6.92	6	4.13
		F	0.327	8	5.71	5	1.92
	20	M	1.35	8	24.7	9	3.23
		F	1.14	12	22.5	6	1.82

F: female; M: male; M1: metabolite MDPC0001, a carboxylic acid derivative; M2: metabolite MDPC0002, N-desmethyl

enzalutamide; NA: not applicable.

† Enzalutamide was formulated as Labrasol solution in all dose groups.

‡ Metabolite ratio = (Metabolite AUC_{24h}/enzalutamide AUC_{24h}) × 100, expressed as %.

§ Accumulation index = (AUC_{24h} at week 26/AUC_{24h} on day 1).

At 20 mg/kg per day, the sex-combined mean C_{max} and AUC_{24h} exposures for enzalutamide were 16.9 µg/mL and 317 µg•h/mL, respectively and the sex-combined C_{max} and AUC_{24h} exposures for the active metabolite M2 was 1.3 µg/mL and 23.6 µg•h/mL, respectively. At 20 mg/kg per day the exposure for enzalutamide in non-Tg rasH2 mice was similar to the clinical exposure in metastatic CRPC patients receiving 160 mg of enzalutamide, daily (C_{max}, 16.6 µg/mL and AUC_{24h}, 322 µg•h/mL), while the exposure of the active metabolite M2 in non-Tg rasH2 mice was from 0.08- to 0.11-fold of that in humans.

2.2.5. Ecotoxicity/environmental risk assessment

No new environmental risk assessment report of enzalutamide was submitted in support of the present extension of indication.

2.2.6. Discussion on non-clinical aspects

No additional nonclinical pharmacology studies were required for this application since the previous submissions were sufficient in this aspect.

The MAH submitted the results of a new pharmacokinetic study assessing in vitro plasma protein binding of enzalutamide, metabolite MDPC0001, a carboxylic acid derivative (M1) and metabolite MDPC0002, desmethyl-enzalutamide (M2) in nontransgenic littermates of transgenic rasH2 mouse (non-Tg rasH2 mouse) and Wistar Hanover (WH) rat plasma (Study 9785-ME-0045). Overall, the plasma protein binding of enzalutamide and the metabolites M1 and M2 in nontransgenic littermates of Tg rasH2 mice and WH rats were comparable to the other rodent strains used in previously submitted toxicology studies. Plasma protein binding was also comparable between rodents and humans.

With regards to carcinogenicity, the daily oral administration of enzalutamide for 26 weeks did not demonstrate any neoplastic findings, indicative of a lack of carcinogenic potential in the Tg rasH2 mice at a dose of ≤ 20 mg/kg per day. However, taking into account that the plasma exposure levels at 20 mg/kg/day (348 µg.h/mL and 286 µg.h/mL, in females and males respectively) were similar to the clinical exposure in metastatic CRPC patients receiving 160 mg/kg/day (322 µg.h/mL) and, the AUC24h for M1 and M2 ranged from 0.08 to 0.21-fold of those in humans, the carcinogenicity potential of enzalutamide cannot be discarded.

In line with ICH S1A guideline, the MAH was requested to submit the final study report of the 2-year pivotal study (both sexes) in Wistar Han (WH) rats during the procedure. In this study increased incidences of the following tumours were considered treatment-related in male WH rats: Leydig cell tumour in the testis; benign thymoma in the thymus; and urothelial papilloma/carcinoma in the urinary bladder, adenoma of pars distalis in the pituitary and fibroadenoma in the mammary gland. In female WH rats, treatment-related increases in adenoma of pars distalis in the pituitary and benign granulosa cell tumour in the ovary were noted. Except for the urinary bladder, these tumours were observed in organs that are regulated via the hypothalamic-pituitary-gonadal hormone axis and considered to be related to the pharmacological activity of enzalutamide. Leydig cell tumours in rats are generally accepted as not relevant to humans [Cook et al, 1999]. The tumours observed in organs that are regulated via the hypothalamic-pituitary-gonadal hormone axis, induced by non-genotoxic compounds, most likely have low relevance to humans under most exposure conditions because humans are quantitatively less sensitive that rats [Cook et al., 2015].

Urothelial papilloma/carcinoma in the urinary bladder is thought to be induced by continuous local irritation of the epithelium by crystals or calculi that consist of excreted carboxylic acid metabolite. Calculi and crystals were observed in rat urinary bladders. However, no obvious mechanistic rationale to explain specifically this malignancy can be established. At 10, 30 and 100 mg/kg per day, the exposure multiples of enzalutamide in male rats were 0.28-, 0.76- and 1.4-fold, respectively, of the exposure in humans taking enzalutamide 160 mg/day, while those of the inactive carboxylic acid metabolite were 0.17-, 0.44- and 1.7-fold, respectively. At all dose levels, the exposure multiple of the active metabolite, N-desmethyl enzalutamide, in male rats was less than 0.12-fold. In conclusion, taking into account that exposure levels, based on AUC, achieved in the study, for enzalutamide plus its metabolite M2, were less than or similar to those in prostate cancer patients at the recommended dose of 160 mg/day (322 µg.h/mL), urinary bladder carcinogenicity potential of enzalutamide in human cannot be excluded (see section 5.3 of the SmPC).

An updated environrmental risk assessement has not been submitted with the applied extension of indication since the environmental risk assessment provided in the initial marketing authorisation was based in the prevalence of all castration-resistant prostate cancer (including non-metastatic CRPC patients after failure of ADT), and the PECsurfacewater used was calculated using a refined Fpen based on the prevalence of all CRPC. In addition, as part of the post approval commitments after the approval of Xtandi in 2013, a full Phase I and II environmental risk assessment program for enzalutamide was completed, which included a fish sexual development test (OECD 234) to evaluate potential endocrine disruptive properties. The results concluded that the placement of enzalutamide on

the European market constitutes no risk for the environment, including surface waters, groundwater, sediments, and terrestrial compartments or to micro-organisms (procedure nr: EMEA/H/C/002639/IB/0032, doc reference: EMA/CHMP/494205/2016). Therefore, additional studies are not required to support the new extension of indication.

2.2.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package is considered adequate to support this application to extend the indication to patients with non-metastatic castration resistant prostate cancer. Relevant information has been included in the SmPC (see SmPC section 5.3).

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Overview of clinical studies

Study	Phase/Study Design	Population	Efficacy Endpoints		Dose	Number of Randomized Patients (Treated)		
			Primary	Secondary		Enzalutamide	Placebo/ Bicalutamide Control	Total
MDV3100-14 (PROSPER)	Phase 3, randomized, double-blind, placebo-controlled in patients with nonmetastatic CRPC	Patients with nonmetastatic CRPC post-primary ADT	BICR-determined MFS	Key: Time to PSA progression, time to first use of antineoplastic therapy, OS. Other:, time to pain progression, time to first use of cytotoxic chemotherapy, chemotherapy-free disease-specific survival, chemotherapy-free survival, PSA response rates, QoL (FACT-P, EQ-5D-5L, QLQ-PR25)	Enzalutamide 160 mg/day Placebo NA	933 (930)	468 (465) placebo	1401 (1395)
MDV3100-09 (STRIVE)	Phase 2, randomized, double-blind, bicalutamide-controlled in patients with metastatic or nonmetastatic CRPC	Patients with metastatic and patients with nonmetastatic CRPC post-primary ADT	Investigator-determined PFS	rPFS, PSA response, time to PSA progression, best overall soft tissue response, time to ≥ 10 point decline of the FACT-P global score	Enzalutamide 160 mg/day Bicalutamide 50 mg/day	198 (197)	198 (198) bicalutamide	396 (395)

ADT: androgen deprivation therapy; BICR: blinded independent central review; CRPC: castration-resistant prostate cancer; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire; FACT-P: Functional Assessment of Cancer Therapy-Prostate questionnaire; MFS: metastasis-free survival; OS: overall survival; PFS: progression-free survival; PSA: prostate-specific antigen; QLQ-PR25: Quality of Life Questionnaire-Prostate 25; QoL: quality of life; rPFS: radiographic progression-free survival

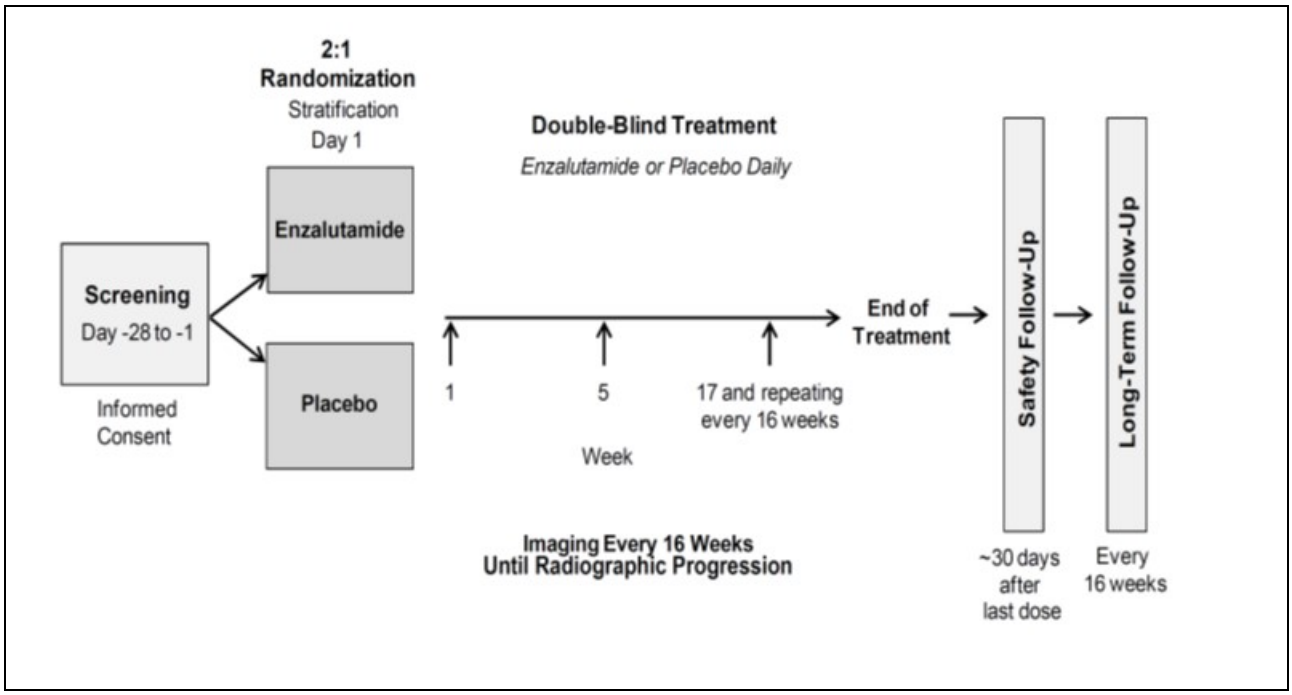
2.4. Clinical efficacy

2.4.1. Main study

MDV3100 14 (PROSPER)

This was a phase 3, randomized, double blind, placebo controlled in patients with nonmetastatic CRPC.

Figure **1. MDV3100-14 Study Schematic**



Patients were screened and randomized 2:1 to enzalutamide or placebo on day 1. While on study drug, patients returned to the study site at weeks 5 and 17 and every 16 weeks thereafter. At week 5, general activities included brief physical examination, assessment of ECOG performance status, adverse events, and concomitant medications reviews, and drug accountability. At week 17 and every 16 weeks thereafter until treatment discontinuation, general activities included radiographic assessments, completion of quality of life questionnaires, study drug dispensing, and central laboratory evaluations (hematology, serum chemistry, and PSA) in addition to the activities performed at week 5. Safety follow-up after permanent treatment discontinuation occurred approximately 30 days after the last dose of study drug or occurred immediately before starting a new antineoplastic treatment if before 30 days after the last dose of study drug.

Methods

Study participants

Eligibility criteria were chosen to include patients with non-metastatic CRPC who progressed on ADT and were at high risk of developing metastases determined by increasing PSA levels as well as a PSA doubling time ≤ 10 months at screening.

Inclusion criteria

- Asymptomatic histologically or cytologically confirmed adenocarcinoma of the prostate
- Ongoing ADT with a LHRH agonist/antagonist or prior bilateral orchiectomy
- Serum testosterone level ≤ 50 ng/dL (1.73 nmol/L) at screening
- PSA doubling time ≤ 10 months at screening
- Progressive disease at study entry while on primary ADT based on rising PSA levels ≥ 2 ng/mL
- No prior or present evidence of metastatic disease
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Exclusion criteria

- Prior use of cytotoxic chemotherapy for prostate cancer
- Participation in a clinical study of an investigational agent that inhibits the AR or androgen synthesis (unless treatment was placebo)
- Prior treatment with hormonal therapy or biologic therapy for prostate cancer, or an investigational agent within 4 weeks before randomization

Treatments

The study drugs included enzalutamide and placebo. The daily dose of enzalutamide/placebo was 160 mg/day given orally in 4 capsules (40 mg each). Dose reduction to 120 or 80 mg/day was allowed.

Patients self-administered blinded study drug orally once daily, with or without food, starting on Day 1. The capsules were swallowed whole without chewing, dissolving, or opening them.

Patients who experienced a Grade 3 or higher toxicity that was attributed to study drug and could not be ameliorated by the use of adequate medical intervention, may have interrupted treatment with blinded study drug for 1 week or until the toxicity grade improved to Grade 2 or lower severity. Subsequently, blinded study drug dosing could be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day) in consultation with the medical monitor.

If blinded study drug was coadministered with a strong cytochrome P450 (CYP) 2C8 inhibitor, the dose of blinded study drug was reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor was discontinued, the blinded study drug dose was returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Objectives

The primary objective of the study was to determine the efficacy of enzalutamide compared with placebo by BICR-assessed MFS.

Key secondary objectives of the study were to evaluate the benefit of enzalutamide compared with placebo as measured by time to PSA progression, time to first use of new antineoplastic therapy, and OS. Other secondary objectives were to compare time to pain progression; time to first use of cytotoxic chemotherapy; chemotherapy-free disease-specific survival; chemotherapy-free survival; PSA response rates; QoL assessed by Functional Assessment of Cancer Therapy – Prostate (FACT P) questionnaire, EQ-5D 5 Dimensions health questionnaire, and (EQ-5D-5L) and Quality of Life Questionnaire Prostate 25 module (QLQ PR25 module); and to evaluate safety between the enzalutamide group and the placebo group.

Outcomes / endpoints

The primary efficacy endpoint was BICR-assessed MFS defined as the time from randomization to radiographic progression, or death within 112 days of treatment discontinuation without evidence of radiographic progression whichever occurred first.

All study films were read locally at the study site and submitted to the central imaging unit for BICR. Each study site designated a radiologist or investigator as the primary imaging reviewer to ensure that all images were read consistently as specified by the protocol.

Table 2. Assessment of Radiographic Progression

	Method of Assessment	Schedule
Bone	A whole-body radionuclide bone scan consisted of 5 regions including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease was defined as the appearance of 1 or more metastatic lesion on bone scan. When bone lesions were found in a single region, confirmation with a second imaging modality (plain film, CT, or MRI) was required. Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan did not require confirmation with a second imaging modality.	Screening and every 16 weeks thereafter (earlier if progression was clinically suspected) until radiographic progression was confirmed by BICR
Soft Tissue	Assessment of soft tissue disease done by CT or MRI. Radiographic progression for soft tissue disease was defined by RECIST 1.1.	

CT=computed tomography; BICR=blinded independent central review; MRI=magnetic resonance imaging; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

Key secondary endpoints included time to PSA progression (time to a 25% or greater increase and an absolute increase of 2 ng/mL), time to first use of new antineoplastic therapy, and Overall Survival.

Additional secondary endpoints included time to pain progression using the BPI-SF; time to first use of cytotoxic chemotherapy; chemotherapy-free disease-specific survival, defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator; chemotherapy-free survival, defined as the time from randomization to the first use of cytotoxic chemotherapy for prostate cancer or death due to any cause; PSA response rate defined as a reduction in PSA of ≥ 50% or ≥ 90% from baseline, or a decline to undetectable levels from baseline; and QoL assessed by FACT-P (additionally for EQ-5D-5L questionnaires and the EORTC QLQ-PR25 module – data not shown).

Sample size

The following assumptions were used in determining the sample size calculation for the MFS endpoint:

- 2:1 enzalutamide to placebo treatment allocation;
- An increasing nonuniform accrual of 0.25 patients per month per site with maximum accrual of 63 patients per month;
- For MFS, a target hazard ratio of 0.72 at a 2-sided significance level of 5% with 90% power. Under an exponential model assumption, the target difference in Kaplan-Meier estimated medians was 9 months (control median of 24 months versus treatment median of 33 months). The median MFS of 24 months for the placebo group was based on published data (Nelson et al, 2009).

A total of 440 MFS events provided 90% power to detect a target hazard ratio of 0.72 based on a 2-sided log-rank test and the overall significance level of 0.05. A sample size of approximately 1305 patients (870 enzalutamide and 435 placebo) was expected to achieve 440 events in approximately 43 months.

Approximately 10% of patients enrolled were expected to be lost to follow-up, found to have metastatic disease at study entry, or have events censored due to required analytical methods, so approximately 1440 patients (960 enzalutamide and 480 placebo) were targeted to be randomized. The time from date of first randomization until 440 MFS events were observed was estimated to be approximately 43 months.

Approximately 500 PSA progression events were expected at the time of the single MFS analysis. Based on a HR assumption of 0.60, this endpoint had >95% power at a 2-sided significance level of 0.02

Approximately 360 new antineoplastic therapy events were expected at the time of the single MFS analysis. This endpoint had 80% power to detect a HR of 0.70 at a 2-sided significance level of 0.02.

At the final analysis of OS (after 3 interim analyses), 590 death events are required to have 85% power to detect a hazard ratio of 0.77 at a 2-sided significance level of 0.05. Under an exponential model assumption, the target difference in Kaplan-Meier estimated medians was expected to be 13.7 months (46 months placebo vs. 59.7 months enzalutamide).

Randomisation

Central randomization to enzalutamide or placebo treatments (2:1) was stratified by the following factors:

- PSA DT (<6 months versus ≥ 6 months)
- Baseline use of a BTA (yes versus no)

Blinding (masking)

This study was blinded and placebo-controlled. All patients, study site personnel (including investigators), and Sponsor staff and its representatives were blinded to treatment assignment.

The blinded control for this study was placebo capsules (placebo) identical in appearance to the enzalutamide capsules.

Statistical methods

The primary analysis population for efficacy was the ITT population, defined as all patients randomly assigned to study treatment, and was based on randomized treatment assignment regardless of whether or not the assigned treatment was administered.

Primary Efficacy Endpoint Analysis: MFS

MFS analyses were performed using a stratified log-rank test to compare the 2 treatment groups using a 2-sided test at a 0.05 level of significance; stratification factors were PSA doubling time and prior or current bone-targeting agent.

Sensitivity analyses were conducted using modified censoring/event rules. These prespecified sensitivity analyses included the following: a modified MFS analysis defined in which disease progression after initiation of any prostate cancer treatment also counted as an event; a modified MFS analysis in which any death, including any posttreatment death, was considered as an event; a modified MFS analysis to assess the sensitivity of MFS to antineoplastic therapy; MFS based on the

investigator assessment; and assessment of the impact of clinical deterioration, defined as permanent discontinuation due to an adverse event (AE), defined by the investigator, prior to protocol-defined evidence of radiographic progression.

Table 3. Censoring Rules

Analysis	Censoring Rules	Date of Censoring
Primary analysis of MFS	Patients with no baseline or no postbaseline assessments	Date of randomization
	Patients who were randomized but confirmed metastatic at baseline by BICR	Date of randomization
	Patients who had no confirmed metastasis as per BICR or did not die prior to data cutoff date	Date of the last radiographic assessment prior to data cutoff date
	Patients who had no confirmed metastasis as per BICR but died after 112 days following last dose of study drug	Date of the last radiographic assessment prior to data cutoff date
	Patients who initiated cytotoxic chemotherapy, abiraterone acetate, or nonradioactive bone-targeting agents without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to first use of any such therapy
	Patients who experienced a skeletal-related event without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest skeletal-related event
	Patients with radiation therapy performed for prostate cancer-related lesions without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest use of radiation therapy
	Patients with 2 or more consecutive missed tumor assessment visits without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the missed visit date
MFS Based on Investigator Assessment	Same as censoring rules for primary analysis of MFS as per Investigator	Same as dates of censoring for primary analysis of MFS as per Investigator
Impact of Antineoplastic	All censoring rules for the primary analysis of MFS	Same as the primary analysis of MFS
Therapies	Patients who initiated any antineoplastic therapy without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to first antineoplastic therapy use
Modified MFS 1 - Including Progression After Alternative Therapy as Event	Patients with no baseline or no postbaseline assessments	Date of randomization
	Patients who had no confirmed metastasis as per BICR but died after 112 days following last dose of study drug	Date of the last radiographic assessment prior to data cutoff date
	Patients who experienced a skeletal-related event without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest skeletal-related event
	Patients with 2 or more consecutive missed tumor assessment visits without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the missed visit date
Modified MFS 2 – Including Post Treatment Deaths as event	Patients with no baseline or no postbaseline assessments	Date of randomization
	Patients who were randomized but confirmed metastatic at baseline by BICR	Date of randomization
	Patients who had no confirmed metastasis as per BICR or did not die prior to data cutoff date	Date of the last radiographic assessment prior to data cutoff date
	Patients who initiated cytotoxic chemotherapy, abiraterone acetate, or nonradioactive bone-targeting agents without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to first use of any such therapy
	Patients who experienced a skeletal-related event without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest skeletal-related event
	Patients with radiation therapy performed for prostate cancer-related lesions without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest use of radiation therapy
	Patients with 2 or more consecutive missed tumor assessment visits without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the missed visit date

BICR=blinded independent central review; MFS=metastasis-free survival.

Prespecified subgroup assessments included the following: PSA doubling time; baseline use of a bone-targeting agent; baseline age; baseline ECOG performance status; geographic region; total Gleason score at diagnosis; and PSA, lactate dehydrogenase (LDH), and hemoglobin levels at baseline.

Key Secondary Efficacy Endpoint Analyses

The primary MFS endpoint was tested at a 0.05 significance level. To maintain the family-wise 2 sided type I error rate at 0.05, if MFS was statistically significant, a parallel testing strategy was used to test OS with allocated type I error rate 0.03 and the remaining key secondary endpoints (time to PSA progression and time to first use of new antineoplastic therapy) with allocated type I error rate 0.02. Time to PSA progression and time to first use of new antineoplastic therapy were tested using a sequential approach, and if both were statistically significant, then the 0.02 alpha was reallocated to OS to allow for OS to be tested at the 0.05 significance level.

Table 4. Key Efficacy Analyses and Multiplicity Adjustment

Order of Testing	Population	Declare Significant	Statistic	Strata
1. Metastasis-free survival[a]	ITT	p <0.05	Stratified log-rank test[b]	• PSA doubling time (<6 months vs ≥6 months) • Prior or current bone-targeting agent (yes vs no)
	ITT, subgroup[b]	NA		
2. Time to PSA progression	ITT	p <0.02	Stratified log-rank test	
3. Time to first use of new antineoplastic therapy	ITT	p <0.02	Stratified log-rank test	
4. Overall survival[c]	ITT	p <0.05 or p <0.03[d]	Stratified log-rank test	

ITT=intent-to-treat; NA=not applicable; PSA=prostate-specific antigen.

a. MFS is the primary analysis.

b. The MFS subgroup analysis was performed with an unstratified log-rank test.

c. Three interim and 1 final analyses were planned for OS; details of each analysis are provided in Section 9.7.4.3.3.

d. If both time to PSA progression and time to first use of new antineoplastic therapy were declared significant, OS was tested at a 0.05 significance level; otherwise, OS was tested at 0.03.

Table 5. Type I Error Spending for the Overall Survival Analyses

		Significance Level	
Analysis	Number of Death Events[a]	Error Rate: 0.03[b]	Error Rate: 0.05[c]
First Interim	135	0.001	0.001
Second Interim	285	0.001	0.002
Third Interim	440	0.009	0.018
Final	596	0.026	0.044

a. Approximate number of targeted events.

b. Used if either time to PSA progression or time to first use of new antineoplastic therapy endpoint failed to show significance. The significance level was fixed at 0.001 for the first interim analysis. For the other analyses, the significance levels will be recalculated based on the actual number of events at each analysis using the O'Brien-Fleming method.[34]

c. Used if both time to PSA progression and time to first use of new antineoplastic therapy endpoint showed significance. The significance level was fixed at 0.001 for the first interim analysis. For the other analyses, the significance levels will be recalculated based on the actual number of events at each analysis using the O'Brien-Fleming method.[34]

The hazard ratio was estimated using a stratified Cox regression model with the same strata as above.

Additional Secondary Endpoint Analyses

A stratified log-rank test was used to compare the 2 treatment groups for time to pain progression, time to first use of cytotoxic chemotherapy, chemotherapy-free disease-specific survival, and chemotherapy-free survival.

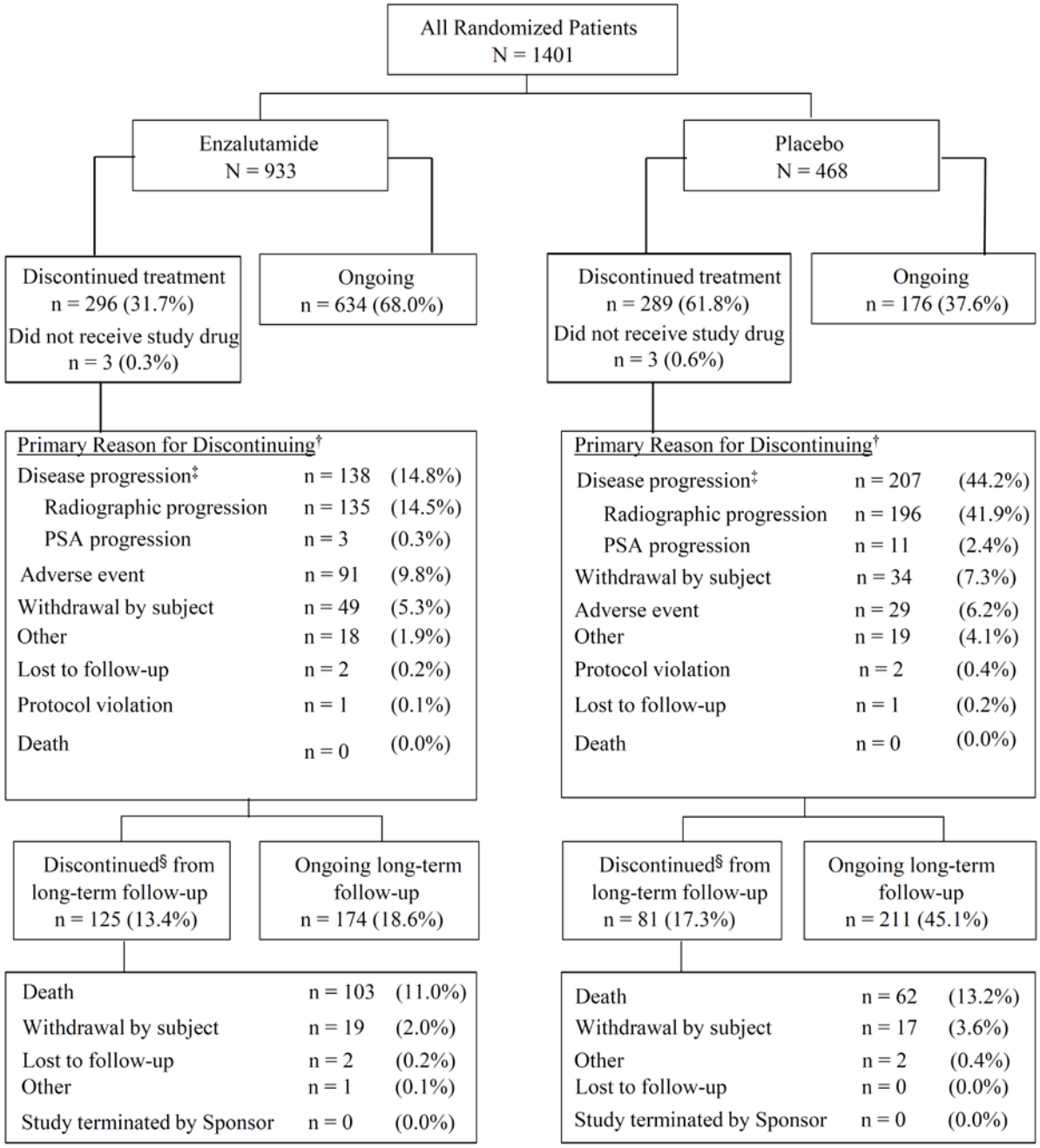
PSA response rate defined as a reduction in PSA of $\geq$ 50% or $\geq$ 90% from baseline or decline to undetectable levels from baseline were each compared between the 2 treatment groups using a stratified Cochran-Masntel-Haenszel mean score test.

All QoL assessment data were summarized descriptively by study visit.

Results

Participant flow

Figure 2. Patient Disposition Flowchart as of 28 June 2017 (ITT Population)



† Primary reason for discontinuation of study drug.

‡ Patients could have been summarized for more than 1 category but were only counted once for each category.

¶ Primary reason for discontinuation of long-term follow-up

Recruitment

Between 26 November 2013 and 28 June 2017, 1401 patients were randomly assigned 2:1 to treatment with enzalutamide (933 patients) or placebo (468 patients); 1395 patients received at least

1 dose or partial dose of enzalutamide (930 patients) or placebo (465 patients). A total of 254 study sites in 32 countries in North and South America, Europe, Australia, New Zealand, and Asia randomized patients in this study. The highest enrolling countries were Australia (136 patients, 9.7%), US (105 patients, 7.5%), Brazil (104 patients, 7.4%), France (103 patients, 7.4%), and Canada (99 patients, 7.1%). Enrollment by site ranged from 1 to 40 patients.

Table 6. Enrollment by Region (ITT Population)

Country	Enzalutamide (N = 933)	Placebo (N = 468)	Total (N = 1401)
North America[a]	141 (15.1%)	63 (13.5%)	204 (14.6%)
Europe[b]	458 (49.1%)	232 (49.6%)	690 (49.3%)
Rest of the world[c]	334 (35.8%)	173 (37.0%)	507 (36.2%)

Source: Table 14.1.2.
Note: Denominator for the percentage was the number of patients in the ITT population for each treatment group and overall.
a. Included United States and Canada.
b. Included European countries Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Poland, Russia, Serbia, Slovakia, Spain, Sweden, Turkey, Ukraine, and United Kingdom.
c. Included Australia, New Zealand, China, Hong Kong, Korea, Malaysia, Singapore, Taiwan, and Thailand, Argentina, Brazil, and Chile.

Conduct of the study

The original study protocol was dated 29 March 2013. There were 3 protocol amendments, which became effective during the study and affected the conduct of the study or planned analyses.

The original statistical analysis plan (SAP), dated 29 March 2013, was amended three times on 16 May 2013 (Version 2), 31 May 2017 (Version 3), and 10 August 2017 (Version 4) to reflect the changes implemented due to the protocol amendments. The main changes in the planned analyses were based on changes made to the protocol, including the timing and plan for the analyses of the primary endpoint of MFS, as well as the secondary endpoints.

A total of 78 patients (5.6%) (54 [5.8%] in the enzalutamide group and 24 [5.1%] in the placebo group) had 1 or more major protocol deviations during the study, defined as deviations of eligibility criteria not met, receiving excluded concomitant medication, receiving the wrong treatment, not receiving required concomitant medication, not discontinuing per the protocol (ie, developed criteria for discontinuation of study drug but did not discontinue study treatment), receiving an incorrect dose, or procedures performed before consent (ie, did not sign informed consent or study-specific procedures were performed before informed consent was signed).

Table 7. Summary of Major Protocol Deviations (ITT Population)

	Enzalutamide (N = 933)	Placebo (N = 468)	Total (N = 1401)
Number of patients with at least one major protocol deviation	54 (5.8%)	24 (5.1%)	78 (5.6%)
Major deviation			
Eligibility criteria were not met	20 (2.1%)	15 (3.2%)	35 (2.5%)
Received excluded concomitant medication	19 (2.0%)	6 (1.3%)	25 (1.8%)
Received the wrong treatment	7 (0.8%)	0 (0.0%)	7 (0.5%)
Did not receive required concomitant medication	5 (0.5%)	1 (0.2%)	6 (0.4%)
Did not discontinue per protocol	2 (0.2%)	0 (0.0%)	2 (0.1%)
Received incorrect dose	1 (0.1%)	1 (0.2%)	2 (0.1%)
Procedures performed before consent	0 (0.0%)	1 (0.2%)	1 (<0.1%)

Source: Table 14.1.13.
Note: Patients 105101, 311101, and 331103 had a protocol deviation in inclusion criterion 9 as reported in the study CRF page. However, the information was not captured in the protocol deviation tracker, hence not accounted for in this output.

Baseline data

Table 8. Key Demographics and Baseline Disease Characteristics in Study MDV3100-14 (ITT Population)

Parameter Statistics/Criteria	**Enzalutamide (n = 933)**	**Placebo (n = 468)**	**Total (n = 1401)**
Age Category (years), n (%)			
< 65	121 (13.0%)	69 (14.7%)	190 (13.5%)
65 to < 75	368 (39.4%)	198 (42.3%)	566 (40.4%)
≥ 75	444 (47.6%)	201 (42.9%)	645 (46.0%)
Age (years)			
Mean (SD)	73.8 (7.83)	72.9 (7.63)	73.5 (7.77)
Median	74.0	73.0	74.0
Minimum, Maximum	50.0, 95.0	53.0, 92.0	50.0, 95.0
Race, n (%)			
Asian	142 (15.2%)	88 (18.8%)	230 (16.4%)
Black or African American	21 (2.3%)	10 (2.1%)	31 (2.2%)
Native Hawaiian or Other Pacific Islander	3 (0.3%)	2 (0.4%)	5 (0.4%)
White	671 (71.9%)	320 (68.4%)	991 (70.7%)
Multiple	4 (0.4%)	4 (0.9%)	8 (0.6%)
Other	15 (1.6%)	5 (1.1%)	20 (1.4%)
Missing	77 (8.3%)	39 (8.3%)	116 (8.3%)
Ethnicity, n (%)			
Hispanic or Latino	76 (8.1%)	37 (7.9%)	113 (8.1%)
Not Hispanic or Latino	784 (84.0%)	392 (83.8%)	1176 (83.9%)
Not Reported/Unknown	73 (7.8%)	39 (8.3%)	112 (8.0%)
Baseline Weight (kg)			
Mean (SD)	84.0 (15.87)	83.6 (16.21)	83.9 (15.98)
Median	82.0	82.0	82.0
Minimum, Maximum	43.1, 149.8	38.0, 167.0	38.0, 167.0
Missing	0	1	1
Body Mass Index (kg/m^2)			
Mean (SD)	28.2 (4.53)	28.2 (4.72)	28.2 (4.60)
Median	27.7	27.5	27.6
Minimum, Maximum	15.8, 51.1	16.9, 51.5	15.8, 51.5
Missing	2	3	5
Baseline ECOG Performance Status, n (%)			
0	747 (80.1%)	382 (81.6%)	1129 (80.6%)
1	185 (19.8%)	85 (18.2%)	270 (19.3%)
> 1	0	0	0
Missing	1 (0.1%)	1 (0.2%)	2 (0.1%)
Baseline Disease Status (by BICR), n (%)			
Nonmetastatic	910 (97.5%)	454 (97.0%)	1364 (97.4%)
Metastatic†	23 (2.5%)	14 (3.0%)	37 (2.6%)
Baseline Prior or Concurrent Use of Bone-Targeting Agents (BTAs)†, n (%)			
No (0)	828 (88.7%)	420 (89.7%)	1248 (89.1%)
Yes	105 (11.3%)	48 (10.3%)	153 (10.9%)
1	103 (11.0%)	47 (10.0%)	150 (10.7%)
2	2 (0.2%)	1 (0.2%)	3 (0.2%)

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Parameter Statistics/Criteria	Enzalutamide (n = 933)	Placebo (n = 468)	Total (n = 1401)
PSA DT Category†, n (%)			
< 6 months	715 (76.6%)	361 (77.1%)	1076 (76.8%)
≥ 6 months	217 (23.3%)	107 (22.9%)	324 (23.1%)
Missing	1 (0.1%)	0	1 (< 0.1)
Stratification‡, n (%)			
PSA DT < 6 months and no BTA	642 (68.8%)	327 (69.9%)	969 (69.2%)
PSA DT < 6 months and BTA	73 (7.8%)	34 (7.3%)	107 (7.6%)
PSA DT ≥ 6 months and no BTA	185 (19.8%)	93 (19.9%)	278 (19.8%)
PSA DT ≥ 6 Months and BTA	32 (3.4%)	14 (3.0%)	46 (3.3%)
Missing	1 (0.1%)	0	1 (< 0.1%)
Baseline PSA DT (months)			
Mean (SD)	4.3 (2.76)	4.3 (3.91)	4.3 (3.19)
Median	3.8	3.6	3.7
Minimum, Maximum	0.4, 37.4	0.5, 71.8	0.4, 71.8
Missing	1	0	1
Baseline Serum PSA (ng/mL)			
Mean (SD)	22.2 (46.14)	22.1 (41.08)	22.2 (44.50)
Median	11.1	10.2	10.7
Minimum, Maximum	0.8, 1071.1	0.2, 467.5	0.2, 1071.1
Missing	0	1	1
Baseline Pain Score As Assessed by Brief Pain Inventory (Short Form) Question #3, n (%)			
0 - 1	639 (68.5%)	336 (71.8%)	975 (69.6%)
2 - 3	106 (11.4%)	52 (11.1%)	158 (11.3%)
> 3	142 (15.2%)	51 (10.9%)	193 (13.8%)
Missing	46 (4.9%)	29 (6.2%)	75 (5.4%)
Baseline FACT-P Global Score			
Mean (SD)	119.5 (17.75)	120.8 (16.73)	120.0 (17.43)
Median	121.0	122.8	121.2
Minimum, Maximum	54.2, 155.0	39.2, 152.0	39.2, 155.0
Missing	46	29	75
Baseline EQ-5D-5L Health Score			
Mean (SD)	76.2 (16.92)	77.5 (15.97)	76.6 (16.61)
Median	80.0	80.0	80.0
Minimum, Maximum	0.0, 100.0	17.0, 100.0	0.0, 100.0
Missing	49	29	78

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
Percentages were based on the number of patients in the ITT population.
BICR: blinded independent central review; BTA: bone-targeting agent; DT: doubling time; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: European Quality of Life 5 Dimensions 5 Levels health questionnaire; FACT-P: Functional Assessment of Cancer Therapy Prostate; ITT: intent-to-treat; PSA: prostate specific antigen
† Patients may have been determined by the BICR to have metastatic disease following entry into the study.
‡ Baseline use of BTA and PSA DT categories were summarized based on data collected in study case report form pages

Table 9. Baseline Disease Characteristics and Prior Therapies for Prostate Cancer for Patients in Study MDV3100-14 (ITT Population)

Parameter Statistics/Criteria	Enzalutamide (n = 933)	Placebo (n = 468)	Total (n = 1401)
Time (months) from initial diagnosis to randomization			
Mean (SD)	99.1 (57.27)	94.1 (56.73)	97.4 (57.12)
Median	90.4	86.8	89.2
Minimum, maximum	2.2, 381.8	2.2, 275.7	2.2, 381.8
Total Gleason score group, n (%)			
Low (2 - 4)	21 (2.3%)	12 (2.6%)	33 (2.4%)
Medium (5 - 7)	491 (52.6%)	230 (49.1%)	721 (51.5%)
High (8 - 10)	381 (40.8%)	207 (44.2%)	588 (42.0%)
Unknown	40 (4.3%)	19 (4.1%)	59 (4.2%)
Number of unique prior prostate cancer therapies, n (%)			
0	32 (3.4%)	24 (5.1%)	56 (4.0%)
1	296 (31.7%)	135 (28.8%)	431 (30.8%)
2	329 (35.3%)	146 (31.2%)	475 (33.9%)
3	179 (19.2%)	94 (20.1%)	273 (19.5%)
≥ 4	97 (10.4%)	69 (14.7%)	166 (11.8%)

Table continued on next page

Parameter Statistics/Criteria	Enzalutamide (n = 933)	Placebo (n = 468)	Total (n = 1401)
Number of unique prior hormonal therapies, n (%)			
0	34 (3.6%)	24 (5.1%)	58 (4.1%)
1	320 (34.3%)	142 (30.3%)	462 (33.0%)
2	339 (36.3%)	151 (32.3%)	490 (35.0%)
3	164 (17.6%)	101 (21.6%)	265 (18.9%)
≥ 4	76 (8.1%)	50 (10.7%)	126 (9.0%)
Prior nonhormonal therapy use, n (%)			
Yes	93 (10.0%)	42 (9.0%)	135 (9.6%)
No	840 (90.0%)	426 (91.0%)	1266 (90.4%)
Use of bone-targeting agents at baseline, n (%)			
Yes	20 (2.1%)	6 (1.3%)	26 (1.9%)
No	913 (97.9%)	462 (98.7%)	1375 (98.1%)
History of radiotherapy, n (%)			
Yes	434 (46.5%)	226 (48.3%)	660 (47.1%)
No	499 (53.5%)	242 (51.7%)	741 (52.9%)
Prior radiotherapy†, n (%)			
External beam	378 (40.5%)	204 (43.6%)	582 (41.5%)
Brachytherapy	40 (4.3%)	25 (5.3%)	65 (4.6%)
Systemic	27 (2.9%)	7 (1.5%)	34 (2.4%)
Type of prior radiotherapy‡, n (%)			
Primary	304 (32.6%)	158 (33.8%)	462 (33.0%)
Palliative	26 (2.8%)	20 (4.3%)	46 (3.3%)
Salvage	114 (12.2%)	52 (11.1%)	166 (11.8%)
History of surgical prostate cancer procedure, n (%)			
Yes	493 (52.8%)	263 (56.2%)	756 (54.0%)
No	440 (47.2%)	205 (43.8%)	645 (46.0%)
Type of prior surgical prostate cancer procedure§, n (%)			
Prostatectomy	234 (25.1%)	139 (29.7%)	373 (26.6%)
Orchiectomy	119 (12.8%)	62 (13.2%)	181 (12.9%)
Transurethral resection of the prostate	83 (8.9%)	35 (7.5%)	118 (8.4%)
Cryoablation	3 (0.3%)	1 (0.2%)	4 (0.3%)
Nephrostomy tube replacement	4 (0.4%)	1 (0.2%)	5 (0.4%)
Other	150 (16.1%)	72 (15.4%)	222 (15.8%)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
ITT: intent-to-treat
†Patients who had more than 1 prior radiotherapy were counted only once at each given category.
‡ Patients who had more than 1 type of prior radiotherapy were counted only once at each given category.
§ Patients who had more than 1 type of prior surgery for prostate cancer were counted only once at each given category.
Source: Study MDV3100-14, Tables 14.1.5 and 14.1.7

Table 10. Prior Drug Therapies for Prostate Cancer (in at Least 1% of Patients in Either Treatment Group) in Study MDV3100-14 (ITT Population)

ATC Level 2 Description Generic Name	Enzalutamide (n = 933)	Placebo (n = 468)	Total (n = 1401)
At least 1 prior therapy, n (%)	901 (96.6%)	444 (94.9%)	1345 (96.0%)
Corticosteroids for Systemic Use, n (%)	18 (1.9%)	8 (1.7%)	26 (1.9%)
Dexamethasone	9 (1.0%)	6 (1.3%)	15 (1.1%)
Drugs for Treatment of Bone Diseases, n (%)	20 (2.1%)	6 (1.3%)	26 (1.9%)
Denosumab	11 (1.2%)	3 (0.6%)	14 (1.0%)
Endocrine Therapy, n (%)	894 (95.8%)	440 (94.0%)	1334 (95.2%)
Bicalutamide	513 (55.0%)	270 (57.7%)	783 (55.9%)
Buserelin	12 (1.3%)	8 (1.7%)	20 (1.4%)
Degarelix	68 (7.3%)	36 (7.7%)	104 (7.4%)
Diethylstilbestrol	15 (1.6%)	8 (1.7%)	23 (1.6%)
Flutamide	102 (10.9%)	45 (9.6%)	147 (10.5%)
Goserelin	337 (36.1%)	185 (39.5%)	522 (37.3%)
Leuprorelin	459 (49.2%)	228 (48.7%)	687 (49.0%)
Nilutamide	24 (2.6%)	12 (2.6%)	36 (2.6%)
Triptorelin	185 (19.8%)	100 (21.4%)	285 (20.3%)
Sex Hormones and Modulators of the Genital System, n (%)	94 (10.1%)	55 (11.8%)	149 (10.6%)
Cyproterone	91 (9.8%)	54 (11.5%)	145 (10.3%)
Urologicals	17 (1.8%)	16 (3.4%)	33 (2.4%)
Tamsulosin	7 (0.8%)	9 (1.9%)	16 (1.1%)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
All prior prostate cancer drug therapies are included. For all percentages, the denominator is the number of patients in the ITT population. Therapeutic class is based on WHO Drug. At each level of summarization (overall, drug class and generic name), patients were counted once only.
ATC: anatomic therapeutic chemical; ITT: intent-to-treat
Source: Study MDV3100-14, Table 14.1.8

Numbers analysed

The final analysis was conducted with 447 MFS events. The data cutoff date for the final analysis was 28 Jun 2017. A total of 1401 patients were randomized between 26 Nov 2013 and 28 Jun 2017 to receive treatment (933 enzalutamide and 468 placebo) and were included in the ITT population. A total of 1395 (99.6%) patients received at least 1 dose of enzalutamide (930 [99.7%] patients) or placebo (465 [99.4%] patients) and were included in the safety population.

A total of 810 (57.8%) patients (634 [68.0%] enzalutamide; 176 [37.6%] placebo) remained on study drug as of the data cutoff date.

Outcomes and estimation

Table 11. Summary of Primary and Secondary Efficacy Results (ITT Population)

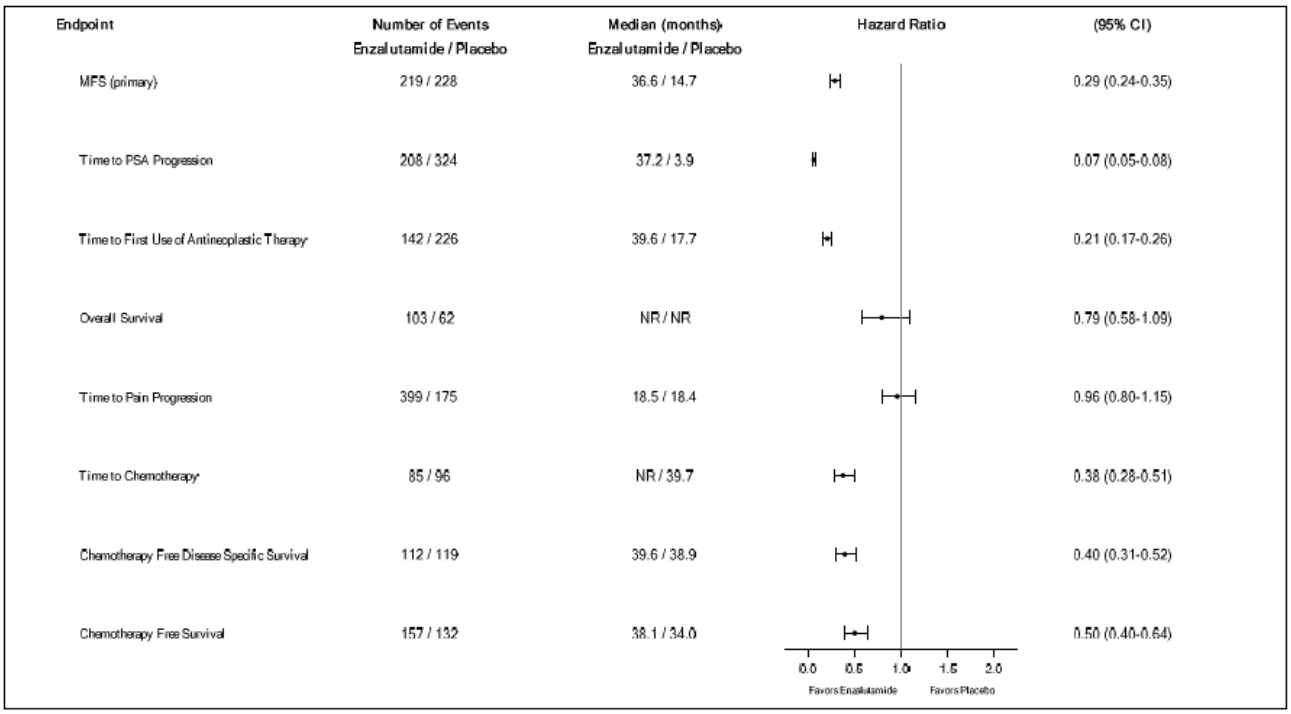
Endpoint	Enzalutamide (N = 933) Events/N (%)	Placebo (N = 468) Events/N (%)
Primary efficacy endpoint		
Metastasis-free survival[†]		
Events (%)	219 (23.5)	228 (48.7)
25th percentile (month)	21.6	7.2
Median (95% CI) (month)	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard ratio (95% CI)‡	0.292 (0.241, 0.352)	
P value‡	< 0.0001	
Key secondary efficacy endpoints		
Time to PSA progression[§]		

Endpoint	Enzalutamide (N = 933) Events/N (%)	Placebo (N = 468) Events/N (%)
Events (%)	208 (22.3)	324 (69.2)
25th percentile (month)	18.5	3.7
Median (95% CI) (month)	37.2 (33.1, NR)	3.9 (3.8, 4.0)
Hazard ratio (95% CI)‡	0.066 (0.054, 0.081)	
P value‡	< 0.0001	
Time to first use of new antineoplastic agent¶		
Events (%)	142 (15.2)	226 (48.3)
25th percentile (month)	30.9	8.8
Median (95% CI) (month)	39.6 (37.7, NR)	17.7 (16.2, 19.7)
Hazard ratio (95% CI)‡	0.208 (0.168, 0.258)	
P value‡	< 0.0001	
Overall survival††		
Events (%)	103 (11.0)	62 (13.2)
25th percentile (month)	NR	34.0
Median (95% CI) (month)	NR (NR, NR)	NR (NR, NR)
Hazard ratio (95% CI)‡	0.795 (0.580, 1.089)	
P value‡	0.1519	
Other secondary efficacy endpoints		
Time to pain progression‡‡		
Events (%)	399 (42.8)	175 (37.4)
25th percentile (month)	7.4	7.4
Median (95% CI) (month)	18.5 (17.0, 22.1)	18.4 (14.8, 22.1)
Hazard ratio (95% CI)‡	0.959 (0.801, 1.149)	
P value‡	0.6534	
Chemotherapy-free disease-specific survival§§		
Events (%)	112 (12.0)	119 (25.4)
25th percentile (month)	33.6	20.5
Median (95% CI) (month)	39.6 (37.7, NR)	38.9 (30.9, 41.3)
Hazard ratio (95% CI)‡	0.398 (0.307, 0.515)	
P value‡	< 0.0001	
Chemotherapy-free survival¶¶		
Events (%)	157 (16.8)	132 (28.2)
25th percentile (month)	28.5	19.0
Median (95% CI) (month)	38.1 (37.7, NR)	34.0 (30.3, 39.7)
Hazard ratio (95% CI)‡	0.504 (0.400, 0.636)	
P value‡	< 0.0001	
Table continued on next page		
Time to first use of cytotoxic chemotherapy†††		
Events (%)	85 (9.1)	96 (20.5)
25th percentile (month)	37.7	23.8
Median (95% CI) (month)	NR (38.1, NR)	39.7 (38.9, 41.3)
Hazard ratio (95% CI)‡	0.378 (0.282, 0.507)	
P value‡	< 0.0001	
Time to degradation of FACT-P global score‡‡‡		
Events (%)	506 (54.2)	239 (51.1)
25th percentile (month)	3.9	4.2
Median (95% CI) (month)	11.1 (11.0, 14.7)	11.1 (11.0, 12.5)
Hazard ratio (95% CI)‡	0.922 (0.787, 1.080)	
P value‡	0.3128	
PSA response rate, Responders/N (%)§§§		
Evaluable patients, n¶¶¶	887	439
Decrease from baseline ≥50%		
Confirmed ≥ 50% PSA responders, n (%)§§§	712 (76.3)	11 (2.4)
95% CI for response rate†††, %	73.5, 79.0	1.2, 4.2
Difference in response rates (95% CI), %	73.96 (70.91, 77.02)	
P value‡‡‡‡	< 0.0001	
Decrease from baseline ≥90%		
Confirmed ≥ 50% PSA responders, n (%)§§§	522 (55.9)	2 (0.4)
95% CI for response rate†††, %	52.7, 59.2	0.1, 1.5
Difference in response rates (95% CI), %	55.52 (52.28, 58.76)	
P value‡‡‡‡	< 0.0001	
Decrease to undetectable		

Endpoint	Enzalutamide (N = 933) Events/N (%)	Placebo (N = 468) Events/N (%)
Confirmed ≥ 50% PSA responders, n (%)§§§	90 (9.6)	0 (0.0)
95% CI for response rate†††† , %	7.8, 11.7	99.2, 100.0
Difference in response rates (95% CI), %	9.65 (7.75, 11.54)	
P value‡‡‡‡	< 0.0001	

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
For all endpoints, number of events observed on or prior to analysis data cutoff date / ITT sample size.
FACT-P: Functional Assessment of Cancer Therapy Prostate; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; PSA: prostate-specific antigen
† Number of earliest contributing events (radiographic progression or death due to any cause within 112 days after treatment discontinuation) observed / ITT sample size.
‡ Hazard ratio and its 95% CI was based on a Cox regression model with treatment group as the only covariate stratified by PSA doubling time and prior or concurrent use of a bone-targeting agent as per IXRS, and was relative to the placebo group with < 1 favoring the enzalutamide group. P value from a stratified log rank test by PSA doubling time and prior or concurrent use of a bone-targeting agent as per IXRS.
§ Based on the Prostate-specific Antigen Progression compliant with Prostate Cancer Clinical Trials Working Group 2 criteria. For patients with PSA declines at week 17, the PSA progression date was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir was documented, which was confirmed by a second consecutive value obtained at least 3 weeks later. For patients without PSA decline at week 17, the PSA progression date was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above baseline was documented, which was confirmed by a second consecutive value at least 3 weeks later. PSA progression could only have been declared on or after the week 17 assessment.
Footnotes continued on next page
¶ Based on the first postbaseline use of antineoplastic therapy for prostate cancer.
†† Number of patients known to have died as of the analysis data cutoff date.
‡‡ Pain progression was defined as a 2-point or greater increase from baseline in the Brief Pain Inventory-Short Form question 3.
§§ Based on the first postbaseline use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator.
¶¶ Based on the first postbaseline use of cytotoxic chemotherapy for prostate cancer or death due to any cause.
††† Based on the first postbaseline use of cytotoxic chemotherapy for prostate cancer.
‡‡‡ Degradation of FACT-P was defined as at least a 10 point decrease from baseline for the global score.
§§§ Confirmation required a subsequent assessment that was consecutive and conducted at least 3 weeks later.
¶¶¶ Evaluable patients for PSA response were patients with a baseline PSA value and at least 1 postbaseline PSA value.
†††† Clopper-Pearson exact binomial CI.
‡ ‡ ‡ ‡ P-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.

Figure 3. Forest Plot of All Primary and Secondary Endpoints (ITT Population)



Primary endpoint

Enzalutamide demonstrated a statistically significant 70.8% reduction in the relative risk of an MFS event compared with placebo (HR: 0.292; 95% CI: 0.241, 0.352; 2 sided stratified log-rank test P < 0.0001). The median time to an MFS event was 36.6 months (95% CI: 33.1, not reached) in the enzalutamide group vs 14.7 months (95% CI: 14.2, 15.0) in the placebo group, a difference of 21.9 months. Most of the patients (76.5%) in the enzalutamide treatment group were censored. A total of 219 (23.5%) patients in the enzalutamide group and 228 (48.7%) patients in the placebo group had BICR-assessed MFS events (447 total MFS events). Of the MFS events, soft-tissue disease progression alone (11.7% enzalutamide and 28.2% placebo) was more common than bone progression alone (7.6% enzalutamide and 16.9% placebo) or concurrent bone and soft-tissue progression (0.8% enzalutamide and 2.8% placebo). A total of 32 (3.4%) patients in the enzalutamide group and 4 patients (0.9%) in the placebo group had an MFS event of death on study without documented radiographic progression, and 76.5% of patients in the enzalutamide group and 51.3% of patients in the placebo group were censored. A small proportion of patients in both treatment groups (2.5% enzalutamide vs 3.0% placebo) were censored because patients were randomized but later confirmed by BICR assessment to have metastatic disease before randomization.

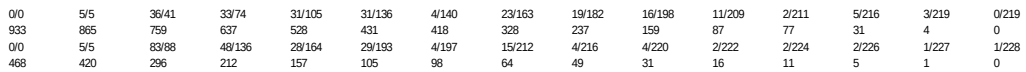
Table 12. MFS - Primary Efficacy Analysis Based on BICR Assessment in Study MDV3100-14 (ITT Population)

	Enzalutamide (n = 933)	**Placebo (n = 468)**
Treatment comparison: enzalutamide vs placebo†		
Hazard ratio (95% CI) ‡	0.292 (0.241, 0.352)	
P value†	< 0.0001	
Metastasis-Free Survival (months)		
25th percentile	21.6	7.2
Median (95% CI)	36.6 (33.1, NR)	14.7 (14.2, 15.0)
75th percentile	NR	33.0
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	18.5	15.1
Status of Metastasis-Free Survival follow-up		
Events§, n (%)	219 (23.5%)	228 (48.7%)
Progression by BICR	187 (20.0%)	224 (47.9%)
Bone progression	71 (7.6%)	79 (16.9%)
Soft-tissue progression	109 (11.7%)	132 (28.2%)
Concurrent bone and soft-tissue progression	7 (0.8%)	13 (2.8%)
Death without documented radiographic progression	32 (3.4%)	4 (0.9%)
Censored¶,n (%)	714 (76.5%)	240 (51.3%)
Metastatic randomized	23 (2.5%)	14 (3.0%)
No postbaseline assessments	37 (4.0%)	22 (4.7%)
Missed 2 consecutive scans before PD	4 (0.4%)	2 (0.4%)
New therapy prior to progression	35 (3.8%)	30 (6.4%)
Cytotoxic chemotherapy	9 (1.0%)	8 (1.7%)
Abiraterone acetate	10 (1.1%)	13 (2.8%)
BTA	10 (1.1%)	3 (0.6%)
Radiation therapy	4 (0.4%)	6 (1.3%)
Abiraterone + BTA	1 (0.1%)	0 (0.0%)
Chemotherapy + BTA	1 (0.1%)	0 (0.0%)
Skeletal-related event	14 (1.5%)	3 (0.6%)
Skeletal-related event + initiation of radiotherapy	2 (0.2%)	2 (0.4%)
No metastatic disease at data cutoff date	599 (64.2%)	167 (35.7%)
Probability of being event free at: †		
Year 1 (95% CI)	0.86 (0.83, 0.88)	0.56 (0.51,#0.61)
Year 2 (95% CI)	0.70 (0.66, 0.74)	0.34 (0.28,#0.39)
Year 3 (95% CI)	0.52 (0.45, 0.59)	0.19 (0.11,#0.28)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).

BICR: blinded independent central review; BTA: bone-targeting agent; MFS: metastasis-free survival; NR: not reached; PD: disease progression; PSA: prostate-specific antigen
† Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in [Study MDV3100 14, Figure 14.2.1.1].
‡ P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per interactive voice/web recognition system. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with < 1 favoring the enzalutamide group.
§ Based on earliest contributing event (radiographic progression or death due to any cause within 112 days after treatment discontinuation).
¶ Patients who were not known to have had an MFS event at the time of analysis data cutoff were censored at the date of last assessment showing no objective evidence of radiographic progression prior to initiation of cytotoxic chemotherapy, abiraterone acetate, nonradioactive bone-targeting agent, radiation therapy for prostate cancer, skeletal-related event, or ≥ 2 consecutive missed tumor assessments. Patients who were randomized but later confirmed to have metastatic disease before randomization were censored at the date of randomization.

Figure 4. Kaplan-Meier Plot of MFS Based on BICR Assessment in Study MDV3100-14 (ITT Population)



HR = 0.292; 95% CI: (0.241, 0.352; P < 0.0001). The median (95% CI): enzalutamide 36.6 months (33.1, NR); placebo: 14.7 months (14.2, 15.0); difference of 21.9 months

Secondary endpoints

- Time to PSA Progression

Table 13. Time to PSA Progression – Key Secondary Efficacy Analysis in Study MDV3100-14 (ITT Population)

	Enzalutamide (n = 933)	**Placebo (n = 468)**
Treatment comparison: enzalutamide vs placebo†		
Hazard ratio	0.066 (0.054, 0.081)	
P value†	< 0.0001	
Time to PSA progression‡ (months)		
N	933	468
25th percentile	18.5	3.7
Median (95% CI)	37.2 (33.1, NR)	3.9 (3.8, 4.0)
75th percentile	NR	7.5

	Enzalutamide (n = 933)	Placebo (n = 468)
Median follow-up time based on reverse Kaplan- Meier estimates for all patients (months)	18.4	11.1
Status of PSA follow-up, n (%)		
PSA progression[§]	208 (22.3)	324 (69.2)
Censored[¶]	725 (77.7)	144 (30.8)
Probability of being event free at:		
Year 1 (95% CI)	0.86 (0.83, 0.88)	0.12 (0.09,#0.16)
Year 2 (95% CI)	0.67 (0.63, 0.71)	0.06 (0.03,#0.10)
Year 3 (95% CI)	0.50 (0.42, 0.58)	0

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
ITT: intent-to-treat; IXRS: interactive voice/web recognition system; NR: not reached; PSA: prostate-specific antigen
† P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ⩾ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with < 1 favoring the enzalutamide group.
‡ Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in [Study MDV3100-14, Figure 14.2.2.1].
§ Based on PSA progression compliant with Prostate Cancer Clinical Trials Working Group 2 criteria. For patients with PSA declines at week 17, the PSA progression date was defined as the date that a ⩾ 25% increase and an absolute increase of ⩾ 2 ng/mL above the nadir was documented, which was confirmed by a second consecutive assessment obtained at least 3 weeks later. For patients without PSA decline at week 17, the PSA progression date was defined as the date that a ⩾ 25% increase and an absolute increase of ⩾ 2 ng/mL above baseline was documented, which was confirmed by a second consecutive assessment at least 3 weeks later. PSA progression was only declared on or after the week 17 assessment.
¶ Patients who did not have confirmed PSA progression at the time of analysis data cutoff were censored at date of last assessment indicating no evidence of confirmed PSA progression

Figure 5. Kaplan-Meier Plot of Time to PSA Progression – Key Secondary Efficacy Analysis in Study MDV3100-14 (ITT Population)

0/0	0/0	5/5	43/48	51/99	34/133	5/138	30/168	15/183	10/193	7/200	1/201	6/207	1/208	0/208
933	879	771	635	500	401	386	288	203	137	76	71	24	2	0
0/0	1/1	229/230	62/292	22/314	7/321	0/321	3/324	0/324	0/324	0/324	0/324	0/324	0/324	0/324
468	427	138	56	25	13	13	5	4	3	0	0	0	0	0

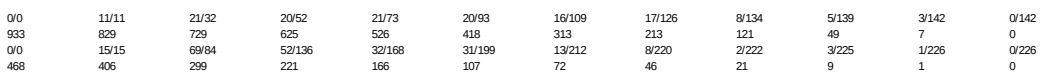
- Time to First Use of New Antineoplastic Therapy

Table 14. Time to First Use of New Antineoplastic Therapy – Key Secondary Efficacy Analysis in Study MDV3100-14 (ITT Population)

	Enzalutamide (n = 933)	**Placebo (n = 468)**
Treatment comparison: enzalutamide vs placebo†		
Hazard ratio (95% CI)[†]	0.208 (0.168, 0.258)	
P value†	< 0.0001	
Time to first use of antineoplastic therapy[‡] (months)		
n	933	468
25th percentile	30.9	8.8
Median (95% CI)	39.6 (37.7, NR)	17.7 (16.2, 19.7)
75th percentile	NR	35.3
Median follow-up time based on reverse Kaplan- Meier estimates for all patients (months)	22.1	22.0
Status of antineoplastic therapy follow-up, n (%)		
Event[§]	142 (15.2)	226 (48.3)
Censored¶	791 (84.8)	242 (51.7)
Probability of being event free at: [‡]		
Year 1 (95% CI)	0.93 (0.91,#0.95)	0.65 (0.60,#0.70)
Year 2 (95% CI)	0.82 (0.79, 0.85)	0.38 (0.32,#0.44)
Year 3 (95% CI)	0.67 (0.60,#0.73)	0.23 (0.14,#0.32)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
IXRS: interactive voice / web recognition system; NR: not reached
† P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ⩾ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with < 1 favoring the enzalutamide group.
‡ Based on estimates. Kaplan-Meier curves are provided in [Study MDV3100 14, Figure 14.2.2.2].
§Calculated as (date of last assessment prior to analysis data cutoff date – randomization date + 1) / 30.4375.
¶ Based on the first postbaseline use of antineoplastic therapy for prostate cancer.
††Patients who had not initiated antineoplastic therapy for prostate cancer at the time of analysis data cutoff were censored at date of last assessment prior to the analysis data cutoff date.

Figure 6. Kaplan-Meier Plot of Time to First Use of New Antineoplastic Therapy – Key Secondary Efficacy Analysis



- Overall Survival

As of the data cutoff date, a total of 165 deaths (approximately 30% of the 596 deaths specified for

the final OS analysis) occurred and included 103 deaths (11.0%) in the enzalutamide group and 62 deaths (13.2%) in the placebo group.

Table 15. Overall Survival – Key Secondary Efficacy Analysis in Study MDV3100-14 (ITT Population)

	Enzalutamide (n = 933)	**Placebo (n = 468)**
Treatment comparison: enzalutamide vs placebo		
Hazard ratio (95% CI)†	0.795 (0.580, 1.089)	
P value†	0.1519	
Overall survival‡ (months)		
25th percentile	NR	34.0
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
75th percentile	NR	NR
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	23.8	23.0
Survival status, n (%)		
Death	103 (11.0%)	62 (13.2%)
Censored§	830 (89.0%)	406 (86.8%)
Alive at data analysis cutoff date	808 (86.6%)	387 (82.7%)
Withdrew consent	19 (2.0%)	17 (3.6%)
Lost to follow-up	2 (0.2%)	0
Other	1 (0.1%)	2 (0.4%)
Probability of being event-free at: ‡		
Year 1 (95% CI)	0.98 (0.96,#0.98)	0.97 (0.95, 0.98)
Year 2 (95% CI)	0.91 (0.88,#0.93)	0.87 (0.82, 0.90)
Year 3 (95% CI)	0.77 (0.71,#0.81)	0.71 (0.62,#0.78)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
IXRS: interactive voice / web recognition system; NR: not reached.
† P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with < 1 favoring the enzalutamide group.
‡Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in [Study MDV3100-14, Figure 14.2.2.3].
§ Patients who were not known to have died at the analysis date were censored at the date last known alive or data analysis cutoff date, whichever occurred first

Figure 7. Kaplan-Meier Plot of Overall Survival – Key Secondary Efficacy Analysis in Study MDV3100-14 (ITT Population)

0/0	6/6	8/14	7/21	16/37	13/50	13/63	16/79	17/96	6/102	1/103	0/103
933	884	805	716	621	521	414	298	169	75	13	0
0/0	0/0	3/3	8/11	8/19	13/32	9/41	7/48	8/56	5/61	1/62	0/62
468	447	403	351	303	247	194	135	78	31	6	0

The predefined number of events for the second interim analysis was 285 and the total number of events reached was 288.

Table 16. Overall Survival in PROSPER at First and Second Interim Analyses

Overall Survival: Interim Analysis	Parameters	Enzalutamide N = 933	Placebo N = 468
First (cutoff date: 28 Jun 2017)	All Events	103 (11.0%)	62 (13.2%)
	Hazard Ratio (95% CI)	0.795 (0.580, 1.089)	
	P-value	0.1519	
	Disease Progression	51 (5.5%)	45 (9.6%)
	Other	49 (5.3%)	16 (3.4%)
	Unknown	3 (0.3%)	1 (0.2%)
Second (cutoff date: 31 May 2018)	All Events	184 (19.7%)	104 (22.2%)
	Hazard Ratio (95% CI)	0.832 (0.654, 1.059)	
	P-value	0.1344	
	Disease Progression	104 (11.1%)	78 (16.7%)
	Other	68 (7.3%)	21 (4.5%)
	Unknown	12 (1.3%)	5 (1.1%)

Post baseline antineoplastic therapy

Table 17. Postbaseline Antineoplastic Therapy with Generic Medication Name Reported for at Least 5% of Patients in Either Treatment Group (Safety Population)

ATC Level 2 Description Generic Name	Enzalutamide (N = 930)	Placebo (N = 465)
Number of patients taking at least 1 postbaseline antineoplastic treatment	244 (26.2%)	258 (55.5%)
Antineoplastic agents[a]	89 (9.6%)	98 (21.1%)
Docetaxel	72 (7.7%)	94 (20.2%)
Corticosteroids for systemic use	36 (3.9%)	65 (14.0%)
Prednisone	21 (2.3%)	38 (8.2%)
Drugs for treatment of bone diseases	44 (4.7%)	64 (13.8%)
Denosumab	25 (2.7%)	38 (8.2%)
Zoledronic acid	21 (2.3%)	26 (5.6%)
Endocrine therapy	167 (18.0%)	185 (39.8%)
Abiraterone	65 (7.0%)	129 (27.7%)
Leuprorelin	49 (5.3%)	21 (4.5%)
Bicalutamide	15 (1.6%)	29 (6.2%)
Sex hormones and modulators of the genital system	23 (2.5%)	56 (12.0%)
Antiandrogens	20 (2.2%)	51 (11.0%)

Source: Table 14.1.12.1.
Note: all postbaseline therapies used to treat prostate cancer which occurred in the study (after starting study drug) were included.
Therapeutic class was based on WHO-DD. At each level of summarization (overall, drug class, and generic name), patients were counted once only.
ATC=anatomic therapeutic chemical; N=number of patients; WHO-DD=World Health Organization Drug Dictionary.
a. Antineoplastic agents included chemotherapies, such as docetaxel, cabazitaxel, carboplatin, capecitabine, cyclophosphamide, cisplatin, and etoposide.

- Time to Pain Progression

Table 18. Time to Pain Progression in Study MDV3100-14 (ITT Population)

	Enzalutamide (n = 933)	**Placebo (n = 468)**
Treatment comparison: enzalutamide vs placebo		
Hazard ratio†	0.959 (0.801, 1.149)	
P value†	0.6534	
Time to pain progression‡ (months)		
25th percentile	7.4	7.4
Median (95% CI)	18.5 (17.0, 22.1)	18.4 (14.8, 22.1)
75th percentile	36.9	NR
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	18.4	11.8
Status of pain assessment§, n (%)		
Pain progression	399 (42.8%)	175 (37.4%)
Censored	534 (57.2%)	293 (62.6%)
Probability of being event-free at: ‡		
Year 1 (95% CI)	0.61 (0.57,#0.65)	0.60 (0.54,#0.65)
Year 2 (95% CI)	0.43 (0.39,#0.47)	0.42 (0.35,#0.48)
Year 3 (95% CI)	0.31 (0.26,#0.38)	0.32 (0.21,#0.43)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
ITT: intent-to-treat; IXRS: interactive voice/web recognition system; NR: not reached; PSA: prostate-specific antigen
† P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with < 1 favoring the enzalutamide group.
‡ Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in [Study MDV3100-14, Figure 14.2.3.1].
§ Pain progression was defined as a ≥ 2-point increase from baseline in the Brief Pain Inventory-Short Form question 3.

Figure 8. Kaplan-Meier Curves for Time to Pain Progression in Study MDV3100-14 (ITT Population)

0/0	4/4	137/141	91/232	56/288	32/320	7/327	30/357	15/372	11/383	9/392	1/393	2/395	4/399	0/399
933	833	621	472	353	280	266	194	138	92	49	46	14	2	0
0/0	5/5	72/77	44/121	19/140	13/153	6/159	8/167	4/171	2/173	0/173	1/174	1/175	0/175	0/175
468	408	286	188	136	104	86	58	43	24	13	11	2	0	0

- Time to First Use of Cytotoxic Chemotherapy

Table 19. Time to First Use of Cytotoxic Chemotherapy in Study MDV3100-14 (ITT Population)

	Enzalutamide (n = 933)	**Placebo (n = 468)**
Treatment comparison: enzalutamide vs placebo		
Hazard ratio†	0.378 (0.282, 0.507)	
P value†	< 0.0001	
Time to first use of cytotoxic chemotherapy‡ (months)		
25th percentile	37.7	23.8
Median (95% CI)	NR (38.1, NR)	39.7 (38.9, 41.3)
75th percentile	NR	41.3
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	22.0	19.4
Status of cytotoxic chemotherapy follow-up, n (%)		
Event§	85 (9.1%)	96 (20.5%)
Censored¶	848 (90.9%)	372 (79.5%)
Probability of being event-free at: ‡		
Year 1 (95% CI)	0.98 (0.96, 0.98)	0.87 (0.83, 0.90)
Year 2 (95% CI)	0.90 (0.87, 0.93)	0.75 (0.69, 0.79)
Year 3 (95% CI)	0.77 (0.70, 0.83)	0.62 (0.52, 0.71)

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
ITT: intent-to-treat; IXRS: interactive voice/web recognition system; NR: not reached; PSA: prostate-specific antigen
† P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with < 1 favoring the enzalutamide group.
‡ Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in [Study MDV3100-14, Figure 14.2.3.4].
§ Based on the first postbaseline use of cytotoxic chemotherapy for prostate cancer
¶ Patients who had not initiated cytotoxic chemotherapy for prostate cancer at the time of analysis data cutoff were censored at date of last assessment prior to the analysis data cutoff date.

Figure 9. Kaplan-Meier Curves for Time to First Use of Cytotoxic Chemotherapy

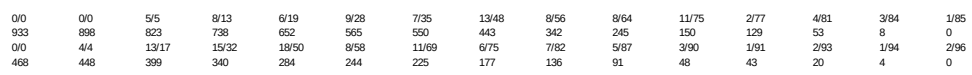


Table 20. Use of Subsequent Therapies in PROSPER at First and Second Interim Analyses

Parameter Statistics	First Analysis		Second Analysis	
	Enzalutamide (n = 933)	Placebo (n = 468)	Enzalutamide (n = 933)	Placebo (n = 468)
Time to first use of new antineoplastic agent†				
Events, n (%)	142 (15.2)	226 (48.3)	231 (24.8)	286 (61.1)
Median (95% CI) (month)	39.6 (37.7, NR)	17.7 (16.2, 19.7)	NR (46.3, NR)	19.0 (17.1, 20.5)
Hazard ratio (95% CI)	0.208 (0.168, 0.258)‡		0.247 (0.207, 0.295) ‡	
P value	< 0.0001‡		< 0.0001‡	
Time to first use of cytotoxic chemotherapy				
Events, n (%)	85 (9.1)	96 (20.5)	140 (15.0)	132 (28.2)
Median (95% CI) (months)	NR (38.1, NR)	39.7 (38.9, 41.3)	NR (NR, NR)	45.4 (42.0, NR)
Hazard ratio (95% CI)	0.378 (0.282, 0.507)‡		0.436 (0.344, 0.554) ‡	
P value	< 0.0001‡		< 0.0001‡	

The first analysis data cutoff date was 28 Jun 2017; the second analysis data cutoff date was 31 May 2018.

CI: confidence interval; NR: not reached

† Based on the first postbaseline use of antineoplastic therapy for prostate cancer.

‡ Hazard ratio and its 95% CI was based on a Cox regression model with treatment group as the only covariate stratified by PSA doubling time and prior or concurrent use of a bone-targeting agent as per IXRS and was relative to the placebo group with < 1 favoring the enzalutamide group. P value from a stratified log-rank test by PSA doubling time and prior or concurrent use of a bone-targeting agent as per IXRS.

Source: PROSPER CSR Tables 30 and 33; PROSPER Second Interim Ad Hoc Tables 14.2.2.2 and 14.2.3.4

Ancillary analyses

Sensitivity analyses

The results of the prespecified sensitivity analyses are presented below.

Figure 10. Forest Plot of MFS - Primary and All Sensitivity Analyses in Study MDV3100-14 (ITT Population)

Ad-hoc analysis of MFS

To further understand the effects of enzalutamide treatment on the development of different types of metastases, an ad hoc analysis of MFS (time to radiographic progression or death) by progression type was conducted to evaluate bone-specific MFS (bMFS) and soft tissue-specific MFS (sMFS). This ad hoc analysis showed a significant benefit in favour of enzalutamide for both bMFS (HR: 0.35, 95% CI: 0.27, 0.46, P < 0.0001) and sMFS (HR: 0.31, 95% CI: 0.25, 0.38, P < 0.0001).

Subgroup analysis - MFS

Figure 11. Forest Plot of MFS - Subgroup Analysis in Study MDV3100-14 (ITT Population)

PSA response rate

The differences in response rates between the enzalutamide and placebo groups for confirmed PSA responses 50% reduction, 90% reduction, and decrease to undetectable levels from baseline were statistically significant (p-values<0.0001 in all rates). The differences in response rates were 73.96% [95% CI: 70.91%-77.02%], 55.52% [95% CI: 52.28%-58.76%], and 9.65% [95% CI: 7.75%-11.54%] for ≥ 50% reduction, ≥ 90% reduction, and decrease to undetectable levels, respectively.

Table 21. PSA Response Rate (Decrease from Baseline) in Study MDV3100-14 (ITT Population)

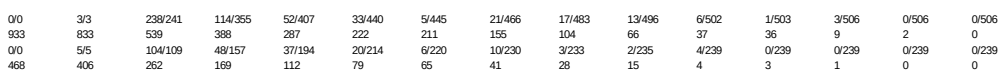
	Enzalutamide (n = 933)	Placebo (n = 468)
Patients with a baseline PSA value, n (%)	933 (100%)	467 (99.8%)
With at least 1 postbaseline PSA assessment	887 (95.1%)	439 (93.8%)
No postbaseline assessment	46 (4.9%)	28 (6.0%)
Number of evaluable patients†	887	439
Confirmed responders (≥ 50% reduction)‡, n (%)	712 (76.3%)	11 (2.4%)
95% CI for response rate§	73.5, 79.0	1.2, 4.2
Difference in response rate (95% CI)¶	73.96 (70.91, 77.02)	
P value††	< 0.0001	
Confirmed Responders (≥ 90% reduction)‡, n (%)	522 (55.9%)	2 (0.4%)
95% CI for response rate§	52.7, 59.2	0.1, 1.5
Difference in response rate (95% CI)¶	55.52 (52.28, 58.76)	
P value††	< 0.0001	
Confirmed responders (decrease to undetectable level)‡, n (%)	90 (9.6%)	0
95% CI for response rate§	7.8, 11.7	99.2, 100.0
Difference in response rate (95% CI)¶	9.65 (7.75, 11.54)	
P value††	< 0.0001	

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
ITT: intent-to-treat; IXRS: interactive voice/web recognition system; PSA: prostate-specific antigen
† Evaluable patients for PSA response are patients with a baseline PSA value and at least 1 postbaseline PSA value.
‡ Confirmaton requires a subsequent assessment that was consecutive and made at least 3 weeks later.
§ Clopper-Pearson exact binomial CI.
¶ Enzalutamide rate minus placebo rate.
†† P value is based on Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.

QoL

Treatment with enzalutamide did not show a significant difference in quality of life compared with placebo as measured by the time to degradation of the FACT-P global score, with a HR of 0.922 [95% CI: 0.787, 1.080]; p-value=0.3128. The median (95% CI) time to degradation of FACT-P was 11.1 months (11.0, 14.7) in the enzalutamide group and similarly 11.1 months (11.0, 12.5) in the placebo group.

Figure 12. Kaplan-Meier Curves for Time to Degradation of the FACT-P Global Score in Study MDV 3100-14 (ITT Population)



HR: 0.922; 95% CI: 0.787, 1.080; P = 0.3128. The median (95% CI): enzalutamide 11.1 months (11.0, 14.7); placebo: 11.1 months (11.0, 12.7).

All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).
The analysis data cutoff date was 28 Jun 2017.
P value was based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS. The HR was based on a Cox regression model (with treatment as the only covariate) stratified by the factors defined above and was relative to placebo with < 1 favoring enzalutamide.
FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; NR: not reached; PSA: prostate-specific antigen.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for trial MDV3100-14

Title: PROSPER: A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer			
Study identifier	C3431005		
Design	Randomised (2:1) phase 3		
	Duration of main phase:		26 November 2013-28 June 2017 (DCO)
Hypothesis	Superiority		
Treatments groups	Enzalutamide		160 mg per day, 933 patients randomised
	Placebo		Placebo, 468 patients randomised
Endpoints and definitions	Primary endpoint	MFS	Time from randomization to the first date of radiographic progression (assessed by BICR) at any time or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first
	Secondary endpoint	Time to PSA progression	Time from randomization to the date of first PSA value demonstrating progression, which was subsequently confirmed
	Secondary endpoint	Time to first use of new antineoplastic therapy	Time from randomization to first use of new antineoplastic for prostate cancer.
	Secondary endpoint	OS	Overall survival. Death any cause
Database lock	28 June 2017		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Enzalutamide	placebo	
	Number of subject	933	468	
	MFS (median; months)	36.6	14.7	
	95%CI	(33.1, NR)	(14.2, 15.0)	

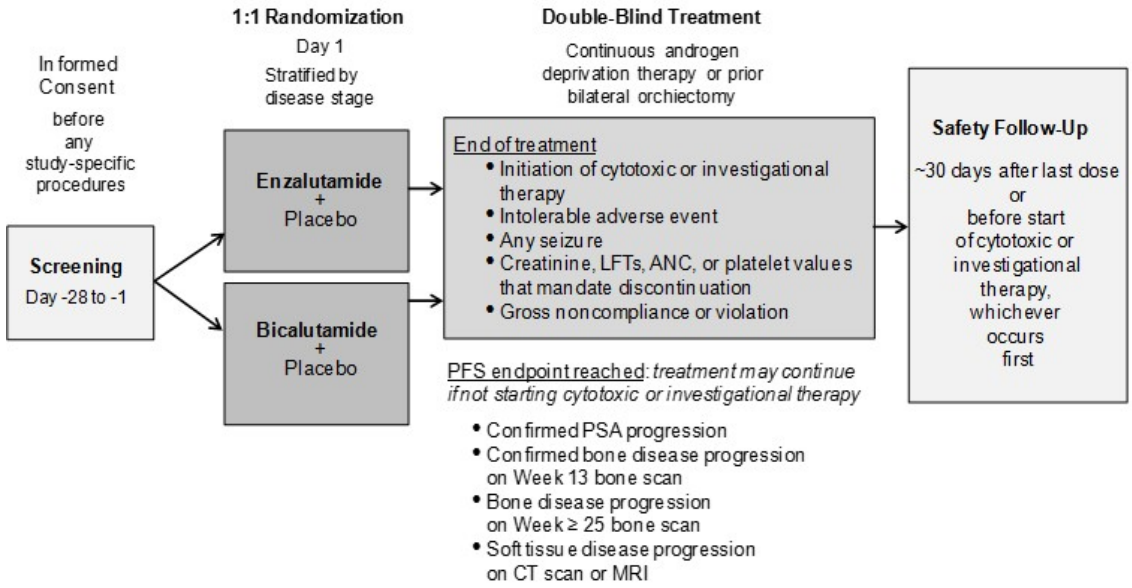
	Time PSA progression (median; months)	37.2	3.9	
	95%CI	(33.1, NR)	(3.8, 4.0)	
	Time antineoplastic agent (median; months)	39.6	17.7	
	95%CI	(37.7, NR)	(16.2, 19.7)	
	OS	NR	NR	
	(median; months)	(NR, NR)	(NR, NR)	
Effect estimate per comparison	Primary endpoint: MFS	Comparison groups	Enzalutamide vs placebo	
		HR	0.292	
		95%CI	(0.241, 0.352)	
		P-value	< 0.0001	
	Secondary endpoint: Time PSA progression	Comparison groups	Enzalutamide vs placebo	
		HR	0.066	
		95%CI	(0.054, 0.081)	
		P-value	< 0.0001	
	Secondary endpoint: Time antineoplastic agent	Comparison groups	Enzalutamide vs placebo	
		HR	0.208	
		95%CI	(0.168, 0.258)	
		P-value	< 0.0001	
	Secondary endpoint: OS	Comparison groups	Enzalutamide vs placebo	
		HR	0.795	
		95%CI	(0.580, 1.089)	
		P-value	0.1519	
Notes	Adjustment for multiplicity was considered for MFS based on BICR assessment, and the key secondary endpoints of time to PSA progression, time to first use of new antineoplastic therapy, and OS			
Analysis description	Hazard ratio and its 95% CI was based on a Cox regression model with treatment group as the only covariate stratified by PSA doubling time and prior or concurrent use of a bone-targeting agent as per IXRS, and was relative to the placebo group with < 1 favoring the enzalutamide group. P value from a stratified log-rank test by PSA doubling time and prior or concurrent use of a bone-targeting agent as per IXRS			

Supportive study

Study MDV3100-09 (STRIVE)

Study MDV3100 09 was a phase 2, randomized, double-blind, multicenter, efficacy and safety study of enzalutamide (160 mg/day) vs bicalutamide (50 mg/day) in patients with nonmetastatic or metastatic CRPC. The study enrolled 396 patients (198 enzalutamide and 198 bicalutamide) at 62 sites in the US. The primary objective of the study was to determine the benefit of enzalutamide compared with bicalutamide by investigator-assessed PFS. The secondary objectives were to determine the benefit of enzalutamide compared with bicalutamide as assessed by time to PSA progression, PSA response, rPFS, objective response rate (metastatic subgroup only) and QoL as assessed by FACT-P; and to determine the safety of enzalutamide compared with bicalutamide

Figure 13. MDV3100-09 Study Schematic for the Double-Blind Treatment Period



ANC: absolute neutrophil count; CT: computed tomography; LFT: liver function test; MRI: magnetic resonance imaging; PFS: progression-free survival; PSA: prostate-specific antigen

Eligible patients were randomly assigned in blinded fashion to receive either enzalutamide or bicalutamide in a 1:1 ratio by central randomization and stratified by disease stage as follows:

- No distant metastasis and no regional nodal metastasis
- No distant metastasis, but presence of regional nodal metastasis, defined as involvement of nodes below the aortic bifurcation
- Presence of distant metastasis (could include nodal involvement above the aortic bifurcation)

Patients without a prior bilateral orchiectomy continued to receive ADT with an LHRH analogue in the absence of intolerable drug related toxicity. Patients were permitted to continue study drug upon disease progression (defined by PSA or radiographic progression) unless they started cytotoxic chemotherapy, new investigational therapy, or an AR inhibitor.

After the first 29 patients were enrolled, the protocol was amended to remove the requirement of a history of definitive localized therapy and to exclude the use of systemic corticosteroids for the treatment of prostate cancer. After the study was unblinded, the protocol was amended to include an open label treatment period as an option for patients on study drug at the time of unblinding and (upon successful screening) for those patients who discontinued bicalutamide before unblinding. This open-label extension study is ongoing.

A safety follow-up visit occurred 30 days after the last dose or prior to initiation of a subsequent cytotoxic or investigational therapy, whichever occurred first.

- Primary endpoint: PFS (defined as the time from randomization to the earliest objective evidence of radiographic progression, PSA progression or death on study [due to any cause, occurring up to and including 30 days after study drug discontinuation])
- Key secondary endpoints:
  - time to PSA progression

- PSA response ≥ 50%
- duration of rPFS (defined as the time from randomization to the earliest objective evidence of radiographic progression or death on study, as assessed by the investigator; prespecified for the nonmetastatic and metastatic subgroups and alpha-protected for the metastatic subgroup)

The positive effect of enzalutamide treatment was shown in both the overall ITT population and the nonmetastatic disease subgroup.

Table 23. Summary of Efficacy Results in Overall ITT Population and Nonmetastatic Disease Subgroup of Study MDV3100-09

	ITT Population		**Nonmetastatic Disease Subgroup**	
Endpoint Statistics	**Enzalutamide 160 mg/day (n = 198)**	**Bicalutamide 50 mg/day (n = 198)**	**Enzalutamide 160 mg/day (n = 70)**	**Bicalutamide 50 mg/day (n = 69)**
PFS† (months)‡				
Median (95% CI)	19.4 (16.5, NR)	5.7 (5.6, 8.1)	NR (19.4, NR)	8.6 (8.1, 11.1)
Hazard ratio (95% CI)§	0.240 (0.181, 0.320)		0.243 (0.142, 0.416)	
P value¶	< 0.0001		< 0.0001	
rPFS†† (months)‡				
Median (95% CI)	NR (NR, NR)	11.2 (8.4, 16.6)	NR (NR, NR)	NR (14.1, NR)
Hazard ratio (95% CI)§	0.303 (0.207, 0.443)		0.238 (0.102, 0.558)	
P value¶	< 0.0001		0.0003	
Time to PSA progression (months)‡				
Median (95% CI)	NR (19.4, NR)	8.3 (5.7, 8.5)	NR (19.4, NR)	11.1 (8.4, 13.9)
Hazard ratio (95% CI)§	0.190 (0.137, 0.264)		0.182 (0.098, 0.341)	
P value¶	< 0.0001		< 0.0001	
PSA response rate				
Confirmed ≥ 50% decrease, n (%)	156 (81.3)	61 (31.3)	60 (90.9)	29 (42.0)
Difference in response rates (95% CI)‡‡	50.0 (41.4, 58.5)		48.9 (35.3, 62.4)	
P value§§	< 0.0001		< 0.0001	

All patients randomly assigned to study treatment (ITT population) and patients in the ITT population with nonmetastatic castrate-resistant prostate cancer at baseline.
The analysis data cutoff date was 09 Feb 2015.
HR: hazard ratio; ITT: intent-to-treat; NR: not reached; PFS: progression-free survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival
† Based on the earliest occurrence of PSA progression, radiographic progression, or death on study (death due to any cause up to and including 30 days after treatment discontinuation).
‡ Based on Kaplan-Meier estimates.
§ HR for the ITT population was based on a Cox regression model (with treatment as the only covariate) stratified by disease stage at study entry and was relative to bicalutamide with < 1 favoring enzalutamide. HR for the nonmetastatic disease subgroup was based on an unstratified Cox regression model (with treatment as the only covariate).
P value for ITT population was based on a log-rank test stratified by disease stage (nonmetastatic, metastatic) at study entry. P value for the nonmetastatic disease subgroup was based on an unstratified log-rank test.
†† Patients who were not known to have had radiographic progression at the time of the analysis data cutoff date were censored at the date of last radiographic assessment prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, treatment discontinuation, and 2 or more consecutive missed tumor assessments.
‡‡ Enzalutamide minus bicalutamide rate.
§§ P-value for ITT population was based on Cochran-Mantel-Haenszel mean score test stratified by disease stage at study entry. P-value for nonmetastatic disease subgroup was based on an unstratified Cochran-Mantel-Haenszel mean score test.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Enzalutamide is currently approved for the treatment of patients with metastatic CRPC (pre and post chemotherapy). The MAH is seeking a broad indication in the treatment of patients with CRPC for which has submitted the results of two clinical studies: a pivotal, randomized, double-blind, placebo-controlled, phase 3 Study MDV3100-14 (PROSPER) conducted in patients with nonmetastatic CRPC, together with supporting data from the nonmetastatic disease subgroup of the randomized, double-blind, bicalutamide-controlled, phase 2 study MDV3100-09 (STRIVE).

Focusing on the main study, the inclusion/exclusion criteria allowed the inclusion of patients on treatment with androgen deprivation therapy with a GnRH agonist/antagonist or prior bilateral orchiectomy, but castration resistant in terms of PSA progression (M0CRPC) at high risk as defined by PSADT < 10 months. Precisely, the definition of this high risk population seems to be the reason for treating with enzalutamide, given the higher risk of developing metastases and eventually the potential impact in both, OS and QoL. Therefore, a more precise definition of patients to be treated with enzalutamide has been included in the section 4.1 of the SmPC.

MFS was chosen as primary endpoint. From a patient perspective, and clinical view, the use of this variable is acknowledged (see also SAG discussion). The fact of being able to delay the onset of metastases represents a valuable objective. Nonetheless, given that the vast majority of these metastases in prostate cancer are asymptomatic, other variables should be kept in mind. Indeed, the fact of delaying the onset of metastasis has not been linked with an increase in OS. As a consequence, besides time to PSA progression and time to first use of new antineoplastic therapy, OS along with time to pain progression and time to first use of cytotoxic chemotherapy, were also included.

The methods to analyse the primary and secondary endpoints seem, overall, acceptable. The company has partially followed the CHMP's SA in relation to the primary endpoint. BICR assessment was recommended.

The sample size calculation and assumptions were not very challenging, with an expected HR of 0.72. Of note, the study was powered to find differences in time to PSA progression and OS.

The blind design of the study, even supported, could pose challenges, taking into account the comparator arm and the PSA progression. Nevertheless, as the primary endpoint was evaluated by a BICR, this was accepted.

Stratification factors are also agreed, although a region stratum should have been included. In this regard, is reassuring that the subgroups analysis on MFS did not show important differences according to regions.

The phase 2 supportive study (STRIVE) was designed in a different population, with metastatic and no metastatic patients, with bicalutamide as comparator. Despite that disease stage was a stratification factor, the value of this study is clearly limited, since the prognosis in the subset of M0 seemed better than in the pivotal trial (few patients in high risk of developing metastasis).

Efficacy data and additional analyses

In the PROSPER trial, a total of 254 study sites in 32 countries in North and South America, Europe, Australia, New Zealand, and Asia randomized patients. The highest enrolling countries were Australia (136 patients, 9.7%), US (105 patients, 7.5%), Brazil (104 patients, 7.4%), France (103 patients,

7.4%), and Canada (99 patients, 7.1%). Subgroups analysis according to geographic region did not reveal any important differences.

The participant flow does no show important concerns and the majority of patients on treatment at the date of the data cutoff, belong to the enzalutamide arm (68% vs 38%). Approximately half of the patients at screening were not randomized.

The study was amended three times. The most important consequence of these amendments was the disconnection between the final MFS and final OS. This change was apparently driven by the results from the study MDV3100-09 (STRIVE study) along with studies MDV3100-03 and 9785-CL-0222. Better outcomes than expected from these ones related to MFS, led the MAH to decouple OS and MFS.

A total of 78 patients (5.6%) (54 [5.8%] in the enzalutamide group and 24 [5.1%] in the placebo group) had 1 or more major protocol deviations during the study. However, percentages of major protocol deviations seem to be evenly balanced between arms and no important biases have been identified.

The baseline characteristics point out that the majority of patients had a baseline ECOG performance status 0 (80.6%) and PSA DT <6 months (76.8%). The median PSA DT was 3.7 months (range: 0.4 to 71.8 months) across treatment groups. More than half of patients had previously received 2 or more prior hormonal therapies in addition to their primary treatment for prostate cancer prior to study entry. The median age at randomization was 74.0 years in the enzalutamide group and 73.0 years in the placebo group. Despite the inclusion criteria, 2.6% of patients were considered metastatic. However, these patients were censored at randomization in the primary MFS analysis and its sensitivity analyses. In any case, due to the small number, no great impact is expected on the results.

Results from PROSPER trial in the efficacy target population of patients at the cut-off date of 28-June-2016 included the main analysis planned for MFS (BIRC assessed) and the first interim analysis for OS (2 IA planned plus 1 final analysis).

With an event rate of 23.5% and 48.7% for enzalutamide and placebo arms respectively, a statistically significant improvement in MFS was observed for enzalutamide compared to placebo (HR: 0.292; 95% CI: 0.241, 0.352). The median MFS (95% CI) was 36.6 months (95% CI: 33.1, NR) in the enzalutamide group and 14.7 months (95% CI: 14.2, 15.0) in the placebo group (Δ 21.9 months). A reduction in both bone metastases and soft tissue metastases was observed among patients treated with enzalutamide compared to placebo. These results are supported by several sensitivity analyses as well as by subgroups analyses.

Overall, key secondary endpoints showed consistency with primary efficacy outcomes. Treatment with enzalutamide delayed time to PSA progression (HR=0.066; 95% CI: 0.054, 0.081) and time to first use of new antineoplastic treatment (HR:0.208; 95% CI: 0.168, 0.258). OS data, still highly immature at the time of the first IA so as to draw any firm conclusion (event rate 11% and 13.2% in enzalutamide and placebo arms respectively), did not cross the boundary for statistical significance (HR=0.795, 95% CI: 0.580, 1.089) and no clear separation of the survival curves is observed, however there is no indication of a detrimental effect, which is reassuring. This remains to be further confirmed (see efficacy conclusions).

Other secondary efficacy endpoints included to provide additional evidence of clinical benefit (need for First Use of Cytotoxic Chemotherapy, Chemotherapy-Free Disease-Specific Survival, Chemotherapy-Free Survival) though still rather immature in some cases, all supported primary efficacy results but time to pain progression (HR=0.959; 95% CI: 0.801, 0.1.149), the latter maybe due to the fact that patients were nonmetastatic at study entry, and therefore were without pain from prostate cancer, and collection of the BPI-SF was discontinued at the time of radiographic progression.

Enzalutamide has shown both in the pre-chemotherapy mildly symptomatic setting and in post-chemotherapy stage to increase the life expectancy. However, this longer survival has not been shown yet in the new setting of M0 CRPC (updated OS are expected). The delay in the onset of metastases does represent a benefit from an individual patient perspective, which is accompanied by a PSA response (see SAG discussion). A direct consequence of these effects is to postpone the use of antineoplastic treatment, which will likely mean to postpone the introduction of new hormonal therapies (e.g. abiraterone) and to a lesser extent the use of docetaxel. In fact, the most common postbaseline antineoplastic therapy was endocrine therapy (18.0% enzalutamide and 39.8% placebo), of which abiraterone was the most common generic name medication (7.0% and 27.7%), followed by leuprorelin (5.3% enzalutamide and 4.5% placebo) and bicalutamide (1.6% enzalutamide and 6.2% placebo). Docetaxel was used by 7.7% vs 20.2% (enzalutamide arms vs placebo respectively). Due to the blinding rules, the treatment for the study participants was blinded until cut-off date, June 2017. Enzalutamide was approved for patients with asymptomatic or minimally symptomatic metastatic CRPC since October 2014. This means that patients in the control arm did not receive enzulatmide after progression, which would have been more in line with current standards. The pivotal trial does not allow establishing if enzalutamide given before or after progression provides greatest benefit to patients (see below).

Splitting the cause of death between disease progression and other causes, showed that a higher percentage of deaths on the placebo group were to disease progression as judged by investigators, 16.7%, as compared to 11.1% in the enzalutamide group. However, the percentage of deaths due to other causes was higher in the enzalutamide group, 8.6%, compared to 5.6% in the placebo group. These differences in deaths due to other causes could be a consequence of the fact that since patients receiving enzalutamide had fewer deaths due to prostate cancer, the likelihood of dying of other causes and comorbidities was higher. However, these analyses are marred by competing risks and can be considered, at best, hypothesis generating. Further long-term efficacy data are expected in order to shed light on that (see efficacy conlcusions).

Treatment with enzalutamide did not show a significant difference in quality of life.

Earlier use of hormonal therapies could impede their efficacy in the metastatic setting, which would pose uncertainties about the right sequence and the consequence of that in terms of mechanism of resistance. PFS2 could partially answer this question, although not included in the design of the PROSPER study. References submitted (Bono et at, 2017 and SPARTAN study) to resolve this issue did not provide enough evidence. Additionally, the present study was not designed to unravel uncertainties about the best possible sequence for enzalutamide treatment. Neither was the study to show the benefit of early versus deferred therapy, i.e. to initiate therapy at the non-metastatic stage versus at time of metastases. Consequently, this cannot be considered clarified with available data. The relative benefit of early versus late use of enzalutamide remains unknown.

Additional expert consultation

A SAG-O meeting was held on September the 6th.

The SAG oncology was invited to provide its opinion on the following points:

1. Do you consider that presently available data are sufficient to demonstrate the clinical benefit of Xtandi in the sought indication, given the absence of documented symptomatic benefit and absence of mature overall survival results?

The effect of enzalutamide in the sought indication is of clear statistical significance. Such an effect is also clinically significant because it is reasonable to assume that postponing the onset of metastasis by 21.9 months (the observed difference in median metastasis-free survival, MFS, between the

experimental and control arm in the pivotal trial) is associated with a delaying of symptoms and worsening of quality of life, and delaying the need for subsequent treatments in the metastatic settings (and associated anxiety in view of the worse prognosis and likely higher toxicity). The results in terms of MFS are corroborated by a trend showing a favourable effect on overall survival (OS), other secondary endpoints, and the effect of enzalutamide in the metastatic setting. The effect of enzalutamide has been consistent across endpoints and stages of the disease in different randomized trials. MFS has been validated as a surrogate endpoint for overall survival in an earlier setting (Xie et al. 2017), which is supportive evidence even acknowledging the different settings and results of the pivotal trial (i.e., the relatively small difference in OS compared to MFS). The toxicity associated with enzalutamide (Grade >3 AEs: 31.4% v. 23.4% for enzalutamide v. placebo, respectively) did not raise particular concerns, as also shown by the low rate of treatment discontinuation (<10% due to toxicity). No significant detriment was observed in quality of life compared to placebo. Thus, the SAG concluded that the clinical benefit has been established based on reasonable assumptions and supportive evidence. This clinical benefit was confirmed from a patient perspective.

However, some SAG members took issue with the lack of a demonstrated effect in terms of quality of life or OS, the lack of long-term follow-up data (including patient-reported outcomes after progression and the objective effects after censoring for the primary endpoint MFS; e.g. PFS 2 like data (response and duration of such therapies). In addition, it would have been of value to have long-term follow-up data on this earlier introduction of enzalutamide in the sequence of currently available treatments. Without having studied the optimal sequence in terms of long-term outcomes leaves a number of uncertainties that make clinical decisions difficult. Although the trend in OS appeared reassuring, further studies would have to determine the clinical usefulness of enzalutamide before v. after evidence of metastasis and symptomatic disease, as well as how early treatment with enzalutamide in the non-metastatic setting fits in the sequence with other agents used in clinical practice according to today's standards. Thus, long-term follow-up at regular interval should be mandated post-approval and further studies are needed to determine optimal sequencing of available treatments. Until further data are available, the value of enzalutamide prior to onset of metastases will be difficult to establish.

2. What is the clinical relevance of a gain in the metastasis-free-survival per se in the setting of non-metastatic CRPC?

MFS is assumed to be associated with a delaying of symptoms and worsening of quality of life, and deferring the need for subsequent treatments in the metastatic settings (and associated anxiety in view of the worse prognosis and likely higher toxicity). All these assumptions are considered quite reasonable given the natural history of the disease, the available therapeutic options in the metastatic setting, and the available supportive data (see answer to question No. 1). In the absence of detrimental toxicity or marked decrease in quality of life due to treatment before development of metastases, delaying metastatic disease can be a valid objective of therapy, shared by both patients and physicians.

These assumptions are difficult to test due to the fact that measuring quality of life and other events is problematic after progression and likely switch to different treatments off-trial. Still, the need for long-term follow-up not just for OS but as much as possible also for symptoms and quality of life cannot be over-emphasized for future drug-developments in this setting.

2.4.3. Conclusions on the clinical efficacy

Results from PROSPER trial are considered to demonstrate a statistically significant advantage in terms of MFS for patients with M0 CRPC. The efficacy results in terms of MFS are also supported by other secondary endpoints. This is considered a clinical benefit per se, in the absence of indications of a

detrimental effect on OS. Thus, the efficacy of enzalutamide in this setting is considered sufficiently demonstrated. Updated OS data are expected.

The CHMP considers the following measure necessary to address issues related to efficacy:

A post-authorisation efficacy study (PAES) in order to investigate the long-term effects of enzalutamide on Overall Survival and relevant secondary endpoints in adult men with high-risk non-metastatic castration-resistant prostate cancer. The MAH should submit the results of the MDV3100-14 (PROSPER) efficacy study.

2.5. Clinical safety

Introduction

The safety profile of enzalutamide in support of its use for the treatment of patients with nonmetastatic castration-resistant prostate cancer (CRPC) is based primarily on the results of the pivotal Study MDV3100-14 (PROSPER), a multinational, phase 3, randomized, double-blind, placebo-controlled study in patients with nonmetastatic CRPC at high risk of disease progression based on rising prostate-specific antigen (PSA) and PSA doubling time.

In addition to Study MDV3100-14, the safety profile of enzalutamide in patients with either nonmetastatic or metastatic CRPC is derived from the following clinical studies involving 5464 patients:

- Two randomized, placebo-controlled, phase 3 studies in chemotherapy-naïve patients with metastatic CRPC (MDV3100-03 [PREVAIL] and 9785-CL-0232 [Asian PREVAIL]). In Study 9785-CL-0232, data from Site 105 was excluded due to data quality.
- One randomized, placebo-controlled, phase 3 study in patients with metastatic CRPC previously treated with docetaxel-based chemotherapy (CRPC2 [AFFIRM]).
- Two randomized, bicalutamide-controlled, phase 2 studies in patients with metastatic CRPC (9785-CL-0222 [TERRAIN]) and with nonmetastatic or metastatic CRPC (MDV3100-09 [STRIVE]). In the study MDV3100-09, 197 patients were treated with enzalutamide (69 nonmetastatic and 128 metastatic) and 198 received bicalutamide (69 nonmetastatic and 129 metastatic).

Together these studies include 3179 patients treated with enzalutamide plus standard of care that make up the integrated safety population. Of the 3179 enzalutamide-treated patients in the integrated safety population, a total of 999 patients (31.4%) had nonmetastatic CRPC and 2180 patients (68.6%) had metastatic CRPC; 2379 patients (74.8%) did not receive prior docetaxel and were considered chemotherapy-naïve and 800 patients (25.2%) had more advanced metastatic CRPC that was previously treated with docetaxel (or another cytotoxic chemotherapy). The dose of enzalutamide in all studies was 160 mg/day orally.

Table 24. Enzalutamide studies included in the Summary of Clinical Safety

Study	Phase/Study Design	Population	Objectives/ Key Endpoints	Dose(s)	Number of Patients who Received Treatment in the Double-blind Phase of the Study		
					Enzalutamide	Placebo/ Bicalutamide Control	Total
MDV3100-14 (PROSPER)	Phase 3, randomized, double-blind, placebo-controlled	CN patients with nonmetastatic CRPC	Efficacy (MFS, TTPSA, TTAnti, OS), safety	enzalutamide 160 mg/day	930	465†	1395
MDV3100-03 (PREVAIL)	Phase 3, randomized, double-blind, placebo-controlled	CN patients with asymptomatic or mildly symptomatic progressive metastatic CRPC	Efficacy (OS, rPFS, TTSRE, TTPSA, TTCC, PSA response), safety	enzalutamide 160 mg/day	871	844†	1715
CRPC2 (AFFIRM)	Phase 3, randomized, double-blind, placebo-controlled	Patients with progressive metastatic CRPC previously treated with docetaxel-based chemotherapy	Efficacy (OS, TTPSA, rPFS, TTSRE), safety, PK,	enzalutamide 160 mg/day	800	399†	1199
9785-CL-0232 (Asian PREVAIL) excluding site 105	Phase 3, randomized, double-blind, placebo-controlled	CN patients with progressive metastatic CRPC with ADT failure	Efficacy (TTPSA, OS, rPFS, TTSRE, TTCC, PSA response), safety, PK	enzalutamide 160 mg/day	198	190†	388
9785-CL-0222 (TERRAIN)	Phase 2, randomized, double-blind, bicalutamide-controlled	CN patients with metastatic CRPC with ADT failure	Efficacy (PFS, rPFS, PSA response, TTPSA), safety	enzalutamide 160 mg/day / bicalutamide 50 mg/day	183	189‡	372
MDV3100-09 (STRIVE)	Phase 2, randomized double-blind, bicalutamide-controlled	CN patients with nonmetastatic or metastatic CRPC with ADT failure	Efficacy (PFS, rPFS, PSA response, TTPSA), safety	enzalutamide 160 mg/day / bicalutamide 50 mg/day	197§	198‡¶	395
Total patients					3179	2285††	5464‡‡,

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.
ADT: Androgen deprivation therapy; CN: chemotherapy naïve; CRPC: castration-resistant prostate cancer; OS: overall survival; PFS: progression-free survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; TTAnti: time to first use of new antineoplastic therapy; TTCC: time to first use of cytotoxic chemotherapy; TTPSA: time to PSA progression; TTSRE: time to skeletal-related event; PK: pharmacokinetics
† Placebo-controlled patients.
‡ Bicalutamide-controlled patients.
§ Includes 69 patients with nonmetastatic disease.
¶ Includes 69 patients with nonmetastatic disease.
†† Includes 387 patients from bicalutamide-controlled studies and 1898 patients from placebo-controlled studies.
‡‡ Data from open-label treatment are excluded from the integrated safety summaries.

Patient exposure

In the MDV3100-14 enzalutamide group, 930 patients received at least 1 dose or partial dose of enzalutamide and 465 received placebo. The median duration of treatment was 18.4 months in the enzalutamide group vs. 11.1 months for the placebo group. Approximately one-third of patients in each treatment group received study drug for ≥ 12 months and < 24 months (33.4% in the enzalutamide group and 32.5% in the placebo group); 35% of patients treated with enzalutamide remained on study drug for at least 2 years compared with 13% of patients in the placebo group.

The extent of exposure to study drug is summarized in Table 23. Extent of exposure

The extent of exposure to enzalutamide in the total enzalutamide group was generally consistent across different subgroups (age, race, geographic region and baseline medical conditions).

Table 25. Extent of exposure

Category	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Treatment duration, months							
Mean (SD)	18.76 (10.67)	13.15 (9.01)	14.87 (9.72)	7.82 (7.30)	14.20 (8.14)	9.25 (6.73)	14.79 (9.54)
Median	18.43	11.07	13.73	4.80	14.03	7.20	13.80
Minimum, Maximum	0, 41.9	0, 42.8	0, 41.9	0, 42.8	0.2, 41.9	0.3, 34.4	0, 41.9
Treatment duration category (months), n (%)							
< 3	46 (4.9%)	25 (5.4%)	264 (9.4%)	505 (26.6%)	33 (8.7%)	63 (16.3%)	297 (9.3%)
≥ 3 to < 6	85 (9.1%)	85 (18.3%)	381 (13.6%)	601 (31.7%)	45 (11.8%)	100 (25.8%)	426 (13.4%)
≥ 6 to < 12	167 (18.0%)	144 (31.0%)	629 (22.5%)	400 (21.1%)	80 (21.1%)	111 (28.7%)	709 (22.3%)
≥ 12 to < 24	311 (33.4%)	151 (32.5%)	982 (35.1%)	304 (16.0%)	176 (46.3%)	98 (25.3%)	1158 (36.4%)
≥ 24	321 (34.5%)	60 (12.9%)	543 (19.4%)	88 (4.6%)	46 (12.1%)	15 (3.9%)	589 (18.5%)
Number of dose modifications (includes interruptions or reductions) n (%)							
0	768 (82.6%)	415 (89.2%)	2407 (86.0%)	1689 (89.0%)	318 (83.7%)	333 (86.0%)	2725 (85.7%)
1	67 (7.2%)	34 (7.3%)	223 (8.0%)	151 (8.0%)	34 (8.9%)	42 (10.9%)	257 (8.1%)
2	43 (4.6%)	7 (1.5%)	86 (3.1%)	38 (2.0%)	17 (4.5%)	8 (2.1%)	103 (3.2%)
3	24 (2.6%)	6 (1.3%)	43 (1.5%)	11 (0.6%)	8 (2.1%)	4 (1.0%)	51 (1.6%)
4	13 (1.4%)	1 (0.2%)	19 (0.7%)	5 (0.3%)	1 (0.3%)	0	20 (0.6%)
5	2 (0.2%)	1 (0.2%)	3 (0.1%)	1 (0.1%)	1 (0.3%)	0	4 (0.1%
6	4 (0.4%)	1 (0.2%)	6 (0.2%)	2 (0.1%)	1 (0.3%)	0	7 (0.2%)
> 6	9 (1.0%)	0	12 (0.4%)	1 (0.1%)	0	0	12 (0.4%)
Number of dose interruptions, n (%)							
0	790 (84.9%)	419 (90.1%)	2436 (87.0%)	1695 (89.3%)	318 (83.7%)	333 (86.0%)	2754 (86.6%)
1	94 (10.1%)	38 (8.2%)	271 (9.7%)	169 (8.9%)	41 (10.8%)	45 (11.6%)	312 (9.8%)
2	25 (2.7%)	5 (1.1%)	51 (1.8%)	26 (1.4%)	16 (4.2%)	8 (2.1%)	67 (2.1%)
3	14 (1.5%)	3 (0.6%)	28 (1.0%)	6 (0.3%)	4 (1.1%)	1 (0.3%)	32 (1.0%)
4	3 (0.3%)	0	7 (0.3%)	1 (0.1%)	1 (0.3%)	0	8 (0.3%)
5	0	0	0	1 (0.1%)	0	0	0
6	2 (0.2%)	0	3 (0.1%)	0	0	0	3 (0.1%)
> 6	2 (0.2%)	0	3 (0.1%)	0	0	0	3 (0.1%)
Reason for dose interruption ¶							
Adverse event	134 (14.4%)	37 (8.0%)	344 (12.3%)	179 (9.4%)	54 (14.2%)	45 (11.6%)	398 (12.5%)
Other	15 (1.6 %)	10 (2.2%)	34 (1.2%)	31 (1.6%)	15 (3.9%)	10 (2.6%)	49 (1.5%)
Number of dose reductions							
0	837 (90.0%)	451 (97.0%)	2664 (95.2%)	1861 (98.1%)	366 (96.3%)	382 (98.7%)	3030 (95.3%)
1	54 (5.8%)	9 (1.9%)	84 (3.0%)	26 (1.4%)	11 (2.9%)	4 (1.0%)	95 (3.0%)
2	23 (2.5%)	2 (0.4%)	29 (1.0%)	5 (0.3%)	2 (0.5%)	1 (0.3%)	31 (1.0%)
3	6 (0.6%)	1 (0.2%)	11 (0.4%)	2 (0.1%)	1 (0.3%)	0	12 (0.4%)
4	3 (0.3%)	2 (0.4%)	3 (0.1%)	3 (0.2%)	0	0	3 (0.1%)
5	4 (0.4%)	0	5 (0.2%)	0	0	0	5 (0.2%)
6	2 (0.2%)	0	2 (0.1%)	0	0	0	2 (0.1%)
> 6	1 (0.1%)	0	1 (0.0%)	1 (0.1%)	0	0	1 (0.0%)
Reason for dose reduction ¶							
Adverse event	90 (9.7%)	12 (2.6%)	128 (4.6%)	34 (1.8%)	13 (3.4%)	4 (1.0%)	141 (4.4%)
Other	9 (1.0%)	2 (0.4%)	15 (0.5%)	6 (0.3%)	2 (0.5%)	1 (0.3%)	17 (0.5%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Treatment duration was defined as [(the date of last dosing)-(the date of first dosing) +1] / 30.4375 for patients who discontinued treatment and [(the cutoff date)-(the date of first dosing) +1] / 30.4375 for patients still on treatment by the cutoff date.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Adverse events

The incidence of any TEAE was lower in the MDV3100-14 enzalutamide group (86.9%) compared with the phase 3 enzalutamide group (93.2%) and total enzalutamide group (93.3%). The incidence of grade ≥ 3 TEAEs was also lower in the MDV3100-14 enzalutamide group (31.4%) compared with the phase 3 enzalutamide group (40.1%) and total enzalutamide group (39.8%) as was the incidence of serious TEAEs (24.3%, 30.7% and 30.6%) and TEAEs leading to death (3.4%, 3.8% and 3.8%).

The proportion of TEAEs in the enzalutamide group of Study MDV3100-14 was higher than in the placebo group (86.9% vs. 77.4%) as was the proportion of TEAEs in the enzalutamide group of the

phase 3 studies vs. the placebo group (93.2% vs. 89.1%). While the within group differences were consistent (the incidences in the enzalutamide groups were higher compared with the placebo groups), in general the magnitude of the difference between the enzalutamide and placebo groups was greater for Study MDV3100-14 than for the phase 3 studies.

Table 26. Overall summary of treatment-emergent adverse events (TEAEs)

	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total
Category, n (%)	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n =1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	Enzalutamide§ (n = 3197)
Any TEAE	808 (86.9%)	360 (77.4%)	2610 (93.2%)	1691 (89.1%)	357 (93.9%)	355 (91.7%)	2967 (93.3%)
TEAE within the first 30 days	468 (50.3%)	180 (38.7%)	1696 (60.6%)	1130 (59.5%)	223 (58.7%)	208 (53.7%)	1919 (60.4%)
TEAE within the first 180 days	692 (74.4%)	289 (62.2%)	2406 (86.0%)	1599 (84.2%)	327 (86.1%)	334 (86.3%)	2733 (86.0%)
TEAE within the first 365 days	758 (81.5%)	339 (72.9%)	2539 (90.7%)	1666 (87.8%)	350 (92.1%)	348 (89.9%)	2889 (90.9%)
TEAE as primary reason for study drug discontinuation¶	87 (9.4%)	28 (6.0%)	230 (8.2%)	154 (8.1%)	29 (7.6%)	24 (6.2%)	259 (8.1%)
TEAE leading to dose interruption of study drug	143 (15.4%)	40 (8.6%)	369 (13.2%)	205 (10.8%)	56 (14.7%)	43 (11.1%)	425 (13.4%)
TEAE leading to dose reduction of study drug	94 (10.1%)	13 (2.8%)	131 (4.7%)	34 (1.8%)	13 (3.4%)	3 (0.8%)	144 (4.5%)
Grade ≥ 3 TEAE††	292 (31.4%)	109 (23.4%)	1121 (40.1%)	695 (36.6%)	143(37.0%)	144 (37.0%)	1264 (39.8%)
Grade ≥ 3 TEAE onset w/in the first 30 days††	37 (4.0%)	12 (2.6%)	190 (6.8%)	152 (8.0%)	28 (7.4%)	28 (7.2%)	218 (6.9%)
Grade ≥ 3 TEAE onset w/in the first 180 days††	135 (14.5%)	51 (11.0%)	634 (22.7%)	551 (29.0%)	85 (22.4%)	103 (26.6%)	719 (22.6%)
Grade ≥ 3 TEAE onset w/in the first 365 days††	193 (20.8%)	79 (17.0%)	875 (31.3%)	641 (33.8%)	115 (30.3%)	133 (34.4%)	990 (31.1%)
Serious TEAE	226 (24.3%)	85 (18.3%)	860 (30.7%)	516 (27.2%)	114 (30.0%)	99 (25.6%)	974 (30.6%)
TEAE leading to death	32 (3.4%)	3 (0.6%)	107 (3.8%)	56 (3.0%)	15 (3.9%)	9 (2.3%)	122 (3.8%)
Study drug-related TEAE‡‡	581 (62.5%)	211 (45.4%)	1796 (64.2%)	954 (50.3%)	243 (63.9%)	200 (51.7%)	2039 (64.1%)
Study drug-related Grade ≥ 3 TEAE††‡‡	113 (12.2%)	25 (5.4%)	296 (10.6%)	138 (7.3%)	41 (10.8%)	29 (7.5%)	337 (10.6%)
Study drug-related serious TEAE‡‡	32 (3.4%)	12 (2.6%)	92 (3.3%)	60 (3.2%)	23 (6.1%)	13 (3.4%)	115 (3.6%)
Study drug-related TEAEs leading to death‡‡	2 (0.2%)	0	3 (0.1%)	1 (0.1%)	3 (0.8%)	0	6 (0.2%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

TEAE: treatment-emergent adverse event; w/in: within

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

¶ TEAE identified as primary reason for study drug discontinuation is from the treatment discontinuation case report form.

††Grade ≥ 3, based on National Cancer Institute-Common Terminology Criteria for Adverse Events, v 4.03.

‡‡ Study drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug or records where the relationship was missing.

Common adverse events

In Study MDV3100-14, TEAEs reported in ≥ 5% of patients in the enzalutamide group are presented by SOC and preferred term [Table 25].

The SOC with TEAEs reported in ≥10% of patients in both treatment groups were General disorders and administration site conditions (47.3% enzalutamide vs. 28.2% placebo), Gastrointestinal disorders (37.8% vs. 31.8%), Nervous system disorders (32.5% vs. 14.8%), Musculoskeletal and connective tissue disorders (30.5% vs. 25.6%), Vascular disorders (26.2% vs. 15.3%), Infections and infestations (24.4% vs. 22.2%), Injury, poisoning and procedural complications (21.1% vs. 11.2%), and Renal and urinary disorders (20.5% vs. 27.1%).

TEAEs most commonly reported (present in ≥ 5% of patients) were fatigue (32.6% enzalutamide vs. 13.8% placebo), hot flush (13.0% vs. 7.7%), hypertension (11.9% vs. 5.2%), nausea (11.4% vs. 8.6%), fall (11.4% vs. 4.1%), dizziness (9.8% vs. 4.3%), decreased appetite (9.6% vs. 3.9%), constipation (9.1% vs. 6.9%), headache (9.1% vs. 4.5%), asthenia (8.8% vs. 6.0%) and weight decreased (5.9% vs. 1.5%).

In the phase 3 studies, TEAEs reported in ≥ 5% of patients in the enzalutamide group were summarized by preferred term (table 26). In Study MDV3100-14, TEAEs occurring in at least 5% of

patients in the placebo group with a ≥ 2% higher incidence than the enzalutamide group were: urinary tract infection (4.1% enzalutamide vs. 6.5% placebo) and urinary retention (2.2% enzalutamide vs. 6.0% placebo).

In Phase 3 studies, 1 TEAE occurred in at least 5% of patients in the placebo group with a ≥ 2% higher incidence than the enzalutamide group: bone pain (7.5% enzalutamide vs. 10.7% placebo).

Table 27. Treatment-emergent adverse events experienced by ≥ 5% of patients in the MDV3100-14 enzalutamide group by SOC and preferred term

	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
SOC (MedDRA v16.1) Preferred Term, n (%)	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3197)
Gastrointestinal Disorders	235 (25.3%)	97 (20.9%)	1103 (39.4%)	700 (36.9%)	115 (30.3%)	134 (34.6%)	1218 (38.3%)
Nausea	**106 (11.4%)**	**40 (8.6%)**	593 (21.2%)	407 (21.4%)	59 (15.5%)	65 (16.8%)	652 (20.5%)
Diarrhoea	91 (9.8%)	45 (9.7%)	416 (14.9%)	241 (12.7%)	38 (10.0%)	45 (11.6%)	454 (14.3%)
Constipation	**85 (9.1%)**	**32 (6.9%)**	502 (17.9%)	302 (15.9%)	43 (11.3%)	58 (15.0%)	545 (17.1%)
General Disorders and Administration Site Conditions	372 (40.0%)	91 (19.6%)	1219 (43.6%)	567 (29.9%)	138 (36.3%)	104 (26.9%)	1357 (42.7%)
Fatigue	**303 (32.6%)**	**64 (13.8%)**	914 (32.7%)	412 (21.7%)	125 (32.9%)	94 (24.3%)	1039 (32.7%)
Asthenia	**82 (8.8%)**	**28 (6.0%)**	356 (12.7%)	171 (9.0%)	22 (5.8%)	13 (3.4%)	378 (11.9%)
Injury, Poisoning and Procedural Complications	106 (11.4%)	19 (4.1%)	256 (9.1%)	69 (3.6%)	39 (10.3%)	23 (5.9%)	295 (9.3%)
Fall	**106 (11.4%)**	**19 (4.1%)**	256 (9.1%)	69 (3.6%)	39 (10.3%)	23 (5.9%)	295 (9.3%)
Investigations	55 (5.9%)	7 (1.5%)	271 (9.7%)	131 (6.9%)	34 (8.9%)	28 (7.2%)	305 (9.6%)
Weight decreased	**55 (5.9%)**	**7 (1.5%)**	271 (9.7%)	131 (6.9%)	34 (8.9%)	28 (7.2%)	305 (9.6%)
Metabolism and Nutrition Disorders	89 (9.6%)	18 (3.9%)	510 (18.2%)	294 (15.5%)	40 (10.5%)	30 (7.8%)	550 (17.3%)
Decreased appetite	**89 (9.6%)**	**18 (3.9%)**	510 (18.2%)	294 (15.5%)	40 (10.5%)	30 (7.8%)	550 (17.3%)
Musculoskeletal and Connective Tissue Disorders	135 (14.5%)	60 (12.9%)	826 (29.5%)	515 (27.1%)	101 (26.6%)	113 (29.2%)	927 (29.2%)
Arthralgia	78 (8.4%)	32 (6.9%)	443 (15.8%)	250 (13.2%)	48 (12.6%)	57 (14.7%)	491 (15.4%)
Back pain	73 (7.8%)	33 (7.1%)	551 (19.7%)	337 (17.8%)	70 (18.4%)	65 (16.8%)	621 (19.5%)
Nervous System Disorders	160 (17.2%)	40 (8.6%)	479 (17.1%)	194 (10.2%)	61 (16.1%)	45 (11.6%)	540 (17.0%)
Dizziness	**91 (9.8%)**	**20 (4.3%)**	241 (8.6%)	103 (5.4%)	40 (10.5%)	29 (7.5%)	281 (8.8%)
Headache	**85 (9.1%)**	**21 (4.5%)**	282 (10.1%)	105 (5.5%)	28 (7.4%)	22 (5.7%)	310 (9.8%)
Renal and Urinary Disorders	62 (6.7%)	36 (7.7%)	201 (7.2%)	116 (6.1%)	22 (5.8%)	19 (4.9%)	223 (7.0%)
Haematuria	62 (6.7%)	36 (7.7%)	201 (7.2%)	116 (6.1%)	22 (5.8%)	19 (4.9%)	223 (7.0%)
Vascular Disorders	209 (22.5%)	58 (12.5%)	686 (24.5%)	211 (11.1%)	99 (26.1%)	60 (15.5%)	785 (24.7%)
Hot Flush	**121 (13.0%)**	**36 (7.7%)**	444 (15.9%)	145 (7.6%)	58 (15.3%)	40 (10.3%)	502 (15.8%)
Hypertension	**111 (11.9%)**	**24 (5.2%)**	302 (10.8%)	72 (3.8%)	50 (13.2%)	24 (6.2%)	352 (11.1%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Events are sorted by SOC alphabetically and then by decreasing frequency of preferred term in the enzalutamide group in MDV3100-14.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Preferred term values highlighted in **BOLD** are TEAEs that occurred in at least 5% of MDV3100-14 enzalutamide group and at least 2% higher than the MDV3100-14 placebo group.

Table 28. Treatment-emergent adverse events experienced by ≥5% of patients in the phase 3 enzalutamide group or in the phase 3 placebo group, by preferred term

Preferred Term (MedDRA v16.1), n (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3197)
Fatigue	303 (32.6%)	64 (13.8%)	**914 (32.7%)**	**412 (21.7%)**	125 (32.9%)	94 (24.3%)	1039 (32.7%)
Nausea	106 (11.4%)	40 (8.6%)	593 (21.2%)	407 (21.4%)	59 (15.5%)	65 (16.8%)	652 (20.5%)
Back pain	73 (7.8%)	33 (7.1%)	551 (19.7%)	337 (17.8%)	70 (18.4%)	65 (16.8%)	621 (19.5%)
Decreased appetite	89 (9.6%)	18 (3.9%)	**510 (18.2%)**	**294 (15.5%)**	40 (10.5%)	30 (7.8%)	550 (17.3%)
Constipation	85 (9.1%)	32 (6.9%)	**502 (17.9%)**	**302 (15.9%)**	43 (11.3%)	58 (15.0%)	545 (17.1%)
Hot flush	121 (13.0%)	36 (7.7%)	**444 (15.9%)**	**145 (7.6%)**	58 (15.3%)	40 (10.3%)	502 (15.8%)
Arthralgia	78 (8.4%)	32 (6.9%)	**443 (15.8%)**	**250 (13.2%)**	48 (12.6%)	57 (14.7%)	491 (15.4%)
Diarrhoea	91 (9.8%)	45 (9.7%)	**416 (14.9%)**	**241 (12.7%)**	38 (10.0%)	45 (11.6%)	454 (14.3%)
Asthenia	82 (8.8%)	28 (6.0%)	**356 (12.7%)**	**171 (9.0%)**	22 (5.8%)	13 (3.4%)	378 (11.9%)
Hypertension	111 (11.9%)	24 (5.2%)	**302 (10.8%)**	**72 (3.8%)**	50 (13.2%)	24 (6.2%)	352 (11.1%)
Headache	85 (9.1%)	21 (4.5%)	**282 (10.1%)**	**105 (5.5%)**	28 (7.4%)	22 (5.7%)	310 (9.8%)
Pain in extremity	32 (3.4%)	12 (2.6%)	280 (10.0%)	191 (10.1%)	35 (9.2%)	20 (5.2%)	315 (9.9%)
Weight decreased	55 (5.9%)	7 (1.5%)	**271 (9.7%)**	**131 (6.9%)**	34 (8.9%)	28 (7.2%)	305 (9.6%)
Oedema peripheral	43 (4.6%)	22 (4.7%)	266 (9.5%)	143 (7.5%)	20 (5.3%)	22 (5.7%)	286 (9.0%)
Musculoskeletal pain	41 (4.4%)	13 (2.8%)	**264 (9.4%)**	**137 (7.2%)**	25 (6.6%)	29 (7.5%)	289 (9.1%)
Fall	106 (11.4%)	19 (4.1%)	**256 (9.1%)**	**69 (3.6%)**	39 (10.3%)	23 (5.9%)	295 (9.3%)
Dizziness	91 (9.8%)	20 (4.3%)	**241 (8.6%)**	**103 (5.4%)**	40 (10.5%)	29 (7.5%)	281 (8.8%)
Anaemia	31 (3.3%)	17 (3.7%)	238 (8.5%)	180 (9.5%)	27 (7.1%)	26 (6.7%)	265 (8.3%)
Vomiting	21 (2.3%)	19 (4.1%)	221 (7.9%)	184 (9.7%)	15 (3.9%)	26 (6.7%)	236 (7.4%)
Bone Pain	11 (1.2%)	6 (1.3%)	210 (7.5%)	204 (10.7%)	15 (3.9%)	14 (3.6%)	225 (7.1%)
Haematuria	62 (6.7%)	36 (7.7%)	201 (7.2%)	116 (6.1%)	22 (5.8%)	19 (4.9%)	223 (7.0%)
Dyspnoea	36 (3.9%)	13 (2.8%)	195 (7.0%)	116 (6.1%)	22 (5.8%)	20 (5.2%)	217 (6.8%)
Insomnia	39 (4.2%)	15 (3.2%)	190 (6.8%)	92 (4.8%)	29 (7.6%)	16 (4.1%)	219 (6.9%)
Urinary tract infection	38 (4.1%)	30 (6.5%)	170 (6.1%)	119 (6.3%)	18 (4.7%)	25 (6.5%)	188 (5.9%)
Cough	29 (3.1%)	15 (3.2%)	162 (5.8%)	105 (5.5%)	15 (3.9%)	16 (4.1%)	177 (5.6%)
Musculoskeletal chest pain	19 (2.0%)	5 (1.1%)	150 (5.4%)	83 (4.4%)	17 (4.5%)	8 (2.1%)	167 (5.3%)
Nasopharyngitis	29 (3.1%)	10 (2.2%)	148 (5.3%)	72 (3.8%)	21 (5.5%)	18 (4.7%)	169 (5.3%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in the phase 3 studies.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Preferred term values highlighted in **BOLD** are TEAEs that occurred in at least 5% of phase 3 enzalutamide group and at least 2% higher than the phase 3 placebo group.

Grade ≥ 3 Treatment-emergent Adverse Events

Overall, the incidence of grade ≥ 3 TEAEs reported in the Study MDV3100-14 was higher in the enzalutamide group than in the placebo group (31.4% vs. 23.4%).

Grade ≥ 3 TEAEs occurring in ≥ 1% of patients in Study MDV3100-14 enzalutamide group and with ≥ 0.5% higher incidence than the placebo group were hypertension (4.6% enzalutamide vs. 2.2% placebo), fatigue (2.9% vs. 0.6%), syncope (1.1% vs. 0.4%), fall (1.3% vs. 0.6%), asthenia (1.2% vs. 0.2%) and pneumonia (1.1% vs. 0.4%). The grade ≥ 3 TEAEs present in ≥ 1% of patients that were lower in the MDV3100-14 enzalutamide group compared with the placebo group were anaemia (1.0% enzalutamide vs. 1.3% placebo), urinary retention (0.4% vs. 1.1%), hydronephrosis (0.1% vs. 0.6%) and general physical health deterioration (0.2% vs. 0.4%) (Table 27).

Overall, the incidence of Grade 3 or higher TEAEs was higher in the enzalutamide group compared with the placebo group during the first 60, 180, and 365 days of treatment.

When adjusted for treatment duration, the event rates per 100 patient-years of treatment for these events were still higher in the enzalutamide group compared with the placebo group.

The overall incidence of grade ≥ 3 TEAEs in the enzalutamide group of Study MDV3100-14 (31.4%) was lower compared with the enzalutamide group of the phase 3 studies (40.1%) and the total enzalutamide group (39.8%). The grade ≥ 3 TEAEs occurring in ≥ 1% of patients that were lower in the MDV3100-14 enzalutamide group compared with the enzalutamide group of the phase 3 studies

were spinal cord compression (0.2% MDV3100-14 enzalutamide vs. 3.1% phase 3) anemia (1.0% vs. 3.7%), back pain (0.2% vs. 2.4%), bone pain (0.1% vs. 1.3%), arthralgia (0.1% vs. 1.3%), general physical health deterioration (0.2% vs. 1.5%) and metastatic pain (0 vs. 1.1%). The lower incidence of these grade ≥ 3 TEAEs in Study MDV3100-14 likely reflects the study population of patients with non-metastatic CRPC.

Table 29. Grade ≥ 3 treatment-emergent adverse events experienced by ≥ 1% of patients in the phase 3 enzalutamide or placebo groups

Preferred Term (MedDRA v16.1), n patients (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Hypertension	**43 (4.6%)**	**10 (2.2%)**	**130 (4.6%)**	**34 (1.8%)**	23 (6.1%)	11 (2.8%)	153 (4.8%)
Fatigue	**27 (2.9%)**	3 (0.6%)	**98 (3.5%)**	**48 (2.5%)**	11 (2.9%)	7 (1.8%)	109 (3.4%)
Haematuria	**16 (1.7%)**	**13 (2.8%)**	43 (1.5%)	32 (1.7%)	7 (1.8%)	6 (1.6%)	50 (1.6%)
Fall	**12 (1.3%)**	3 (0.6%)	**28 (1.0%)**	**9 (0.5%)**	4 (1.1%)	5 (1.3%)	32 (1.0%)
Asthenia	**11 (1.2%)**	**1 (0.2%)**	**46 (1.6%)**	**20 (1.1%)**	4 (1.1%)	3 (0.8%)	50 (1.6%)
Pneumonia	**10 (1.1%)**	**2 (0.4%)**	**38 (1.4%)**	**15 (0.8%)**	6 (1.6%)	5 (1.3%)	44 (1.4%)
Syncope	**10 (1.1%)**	**2 (0.4%)**	31 (1.1%)	14 (0.7%)	4 (1.1%)	8 (2.1%)	35 (1.1%)
Anaemia	9 (1.0%)	6 (1.3%)	104 (3.7%)	76 (4.0%)	10 (2.6%)	10 (2.6%)	114 (3.6%)
Urinary tract infection	7 (0.8%)	3 (0.6%)	33 (1.2%)	18 (0.9%)	2 (0.5%)	7 (1.8%)	35 (1.1%)
Urinary retention	4 (0.4%)	5 (1.1%)	17 (0.6%)	25 (1.3%)	2 (0.5%)	7 (1.8%)	19 (0.6%)
Back Pain	2 (0.2%)	1 (0.2%)	67 (2.4%)	44 (2.3%)	8 (2.1%)	5 (1.3%)	75 (2.4%)
General physical health deterioration	2 (0.2%)	2 (0.4%)	41 (1.5%)	20 (1.1%)	3 (0.8%)	2 (0.5%)	44 (1.4%)
Spinal cord compression	2 (0.2%)	1 (0.2%)	**88 (3.1%)**	**41 (2.2%)**	1 (0.3%)	2 (0.5%)	89 (2.8%)
Arthralgia	1 (0.1%)	1 (0.2%)	35 (1.3%)	20 (1.1%)	6 (1.6%)	4 (1.0%)	41 (1.3%)
Bone Pain	1 (0.1%)	0	37 (1.3%)	39 (2.1%)	2 (0.5%)	4 (1.0%)	39 (1.2%)
Hydronephrosis	1 (0.1%)	3 (0.6%)	8 (0.3%)	24 (1.3%)	9 (2.4%)	9 (2.3%)	17 (0.5%)
Metastatic pain	0	0	30 (1.1%)	19 (1.0%)	3 (0.8%)	2 (0.5%)	33 (1.0%)
Pain in extremity	0	0	19 (0.7%)	21 (1.1%)	3 (0.8%)	1 (0.3%)	22 (0.7%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in MDV3100-14.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Preferred terms highlighted in **BOLD** are grade ≥ 3 TEAEs that occurred in ≥ 1% of patients in the phase 3 enzalutamide group in both the MDV3100-14 and phase 3 columns when there was ≥ 0.5% higher incidence in the enzalutamide group than placebo group.

The system organ classes with Grade 3 or higher TEAEs reported in at least 1% of patients in either treatment group and a 2% higher incidence in the enzalutamide group compared with the placebo group were Vascular disorders (5.6% enzalutamide vs. 3.0% placebo), General disorders and administration site conditions (5.2% vs. 2.2%), Infections and infestations (4.8% vs. 2.2%), and Nervous system disorders (4.0% vs. 1.3%). Renal and urinary disorders (4.9% vs. 7.7%) was the only system organ class with Grade3 or higher TEAEs reported 2% higher in the placebo group compared with the enzalutamide group.

Table 30. Grade 3 or higher Treatment-Emergent Adverse Events by increasing exposure time after initiation of study drug (Safety population)

	Enzalutamide (N = 930)	Placebo (N = 465)
Patients with any Grade ≥3 TEAE, n (%)		
Within first 60 days	65 (7.0%)	16 (3.4%)
Within first 180 days	135 (14.5%)	51 (11.0%)
Within first 365 days	193 (20.8%)	79 (17.0%)
Overall	292 (31.4%)	109 (23.4%)
Time to first Grade ≥3 TEAE (months)		
Events	292 (31.4%)	109 (23.4%)
Censored[a]	638 (68.6%)	356 (76.6%)
25th percentile[b]	13.8	13.7
Median (95% CI)[b]	NR (32.7, NR)	NR (26.9, NR)
75th percentile[b]	NR	NR

Source: Table 14.3.1.3.6, Table 14.3.1.3.8.1, Table 14.3.1.3.8.2, Table 14.3.1.3.8.3, Table 14.3.1.3.8.4, and Table 14.3.1.3.4.
CI=confidence interval; n/N=number of patients; NR=not reached; TEAE=treatment-emergent adverse events
a. Patients who were not known to have had the Grade 3 or higher TEAE by the analysis cutoff date were censored at the end of treatment-emergent period or data cutoff date (whichever was earlier).
b. Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in Figure 14.3.1.3.4.

Study-drug related adverse events

Overall, 581 patients (62.5%) in the enzalutamide group and 211 patients (45.4%) in the placebo group had study drug-related TEAEs. The system organ classes with study drug-related TEAEs reported in the greatest proportion of patients were General disorders and administration site conditions (35.8% enzalutamide vs. 18.1%placebo) and Gastrointestinal disorders (20.3% vs. 16.6%).

Study drug-related TEAEs with at least a 2% higher incidence in the enzalutamide group compared with the placebo group were fatigue (28.2% enzalutamide vs. 11.6%placebo), decreased appetite (8.0% vs. 1.5%), hot flush (10.4% vs. 6.0%), hypertension (6.6% vs. 3.0%), weight decreased (3.7% vs. 0.4%), dizziness (5.8% vs. 2.8%), headache (5.8% vs. 3.0%), nausea (8.0% vs. 5.4%), and asthenia (6.7% vs. 4.1%) [Table 29]. Vomiting was the only study drug related adverse event with a higher incidence in the placebo group (0.4% vs. 0.9%).

The drug-related TEAEs occurring at a higher incidence in the MDV3100-14 enzalutamide group compared with total enzalutamide group included fatigue, hypertension, dizziness, headache and decreased weigh.

Table 31. Study drug-related treatment-emergent adverse events by ≥ 2% of patients in the phase 3 enzalutamide or placebo groups

Preferred Term (MedDRA v16.1), n patients (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§ (n = 3179)
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	
Fatigue	262 (28.2%)	54 (11.6%)	678 (24.2%)	278 (14.6%)	111 (29.2%)	75 (19.4%)	789 (24.8%)
Hot flush	97 (10.4%)	28 (6.0%)	338 (12.1%)	110 (5.8%)	50 (13.2%)	29 (7.5%)	388 (12.2%)
Decreased appetite	74 (8.0%)	7 (1.5%)	253 (9.0%)	127 (6.7%)	21 (5.5%)	17 (4.4%)	274 (8.6%)
Nausea	74 (8.0%)	25 (5.4%)	361 (12.9%)	240 (12.6%)	37 (9.7%)	30 (7.8%)	398 (12.5%)
Asthenia	62 (6.7%)	19 (4.1%)	217 (7.8%)	89 (4.7%)	13 (3.4%)	9 (2.3%)	230 (7.2%)
Hypertension	61 (6.6%)	14 (3.0%)	130 (4.6%)	28 (1.5%)	18 (4.7%)	13 (3.4%)	148 (4.7%)
Dizziness	54 (5.8%)	13 (2.8%)	114 (4.1%)	39 (2.1%)	22 (5.8%)	17 (4.4%)	136 (4.3%)
Headache	54 (5.8%)	14 (3.0%)	124 (4.4%)	41 (2.2%)	14 (3.7%)	15 (3.9%)	138 (4.3%)
Diarrhoea	45 (4.8%)	22 (4.7%)	174 (6.2%)	100 (5.3%)	18 (4.7%)	20 (5.2%)	192 (6.0%)
Weight decreased	34 (3.7%)	2 (0.4%)	80 (2.9%)	35 (1.8%)	13 (3.4%)	11 (2.8%)	93 (2.9%)
Constipation	27 (2.9%)	12 (2.6%)	126 (4.5%)	67 (3.5%)	13 (3.4%)	12 (3.1%)	139 (4.4%)
Arthralgia	21 (2.3%)	9 (1.9%)	68 (2.4%)	38 (2.0%)	5 (1.3%)	10 (2.6%)	73 (2.3%)
Oedema peripheral	20 (2.2%)	7 (1.5%)	83 (3.0%)	34 (1.8%)	5 (1.3%)	3 (0.8%)	88 (2.8%)
Dysgeusia	15 (1.6%)	1 (0.2%)	88 (3.1%)	31 (1.6%)	8 (2.1%)	2 (0.5%)	96 (3.0%)
Insomnia	14 (1.5%)	6 (1.3%)	56 (2.0%)	23 (1.2%)	12 (3.2%)	6 (1.6%)	68 (2.1%)
Vomiting	4 (0.4%)	4 (0.9%)	80 (2.9%)	74 (3.9%)	5 (1.3%)	6 (1.6%)	85 (2.7%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).
The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.
Patients with multiple events for a given preferred term were counted only once for each preferred term. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in MDV3100-14.
Study drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug or records where the relationship was missing.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Adverse events of special interest

The pre-specified TEAEs of interest described are seizure, posterior reversible encephalopathy syndrome (PRES), cognitive and memory impairment, selected fatigue-related events, neutrophil count decreased, hypertension, selected cardiovascular events (major cardiovascular events or MACE), hepatic impairment and second primary malignancies excluding nonmelanoma skin cancer. The additional TEAEs of clinical interest are falls, fractures, syncope, presyncope, loss of consciousness, dizziness, postural dizziness and renal impairment (Table 30. Overall summary of treatment-emergent adverse events of interest).

Table 32. Overall summary of treatment-emergent adverse events of interest

	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total
Category, n (%)	Enzalutamide (n = 930)	Placebo (n =465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	Enzalutamide§ (n = 3179)
Convulsions (seizure)	3 (0.3%)	0	10 (0.4%)	1 (0.1%)	3 (0.8%)	1 (0.3%)	13 (0.4%)
PRES¶	0	0	0	0	0	0	0
Cognitive and memory impairment	48 (5.2%)	9 (1.9%)	136 (4.9%)	29 (1.5%)	19 (5.0%)	5 (1.3%)	155 (4.9%)
Selected fatigue-related events	385 (41.4%)	94 (20.2%)	1265 (45.2%)	597 (31.5%)	144 (37.9%)	110 (28.4%)	1409 (44.3%)
Neutrophil count decreased	8 (0.9%)	1 (0.2%)	39 (1.4%)	11 (0.6%)	5 (1.3%)	0	44 (1.4%)
Falls ††	106 (11.4%)	19 (4.1%)	256 (9.1%)	69 (3.6%)	39 (10.3%)	23 (5.9%)	295 (9.3%)
Fractures ††	104 (11.2%)	26 (5.6%)	285 (10.2%)	84 (4.4%)	43 (11.3%)	27 (7.0%)	328 (10.3%)
Syncope‡‡	12 (1.3%)	4 (0.9%)	34 (1.2%)	17 (0.9%)	4 (1.1%)	8 (2.1%)	38 (1.2 %)
Hypertension	114 (12.3%)	25 (5.4%)	317 (11.3%)	81 (4.3%)	55 (14.5%)	26 (6.7%)	372 (11.7%)
Selected cardiovascular events	48 (5.2%)	13 (2.8%)	126 (4.5%)	50 (2.6%)	24 (6.3%)	11 (2.8%)	150 (4.7%)
Hepatic Impairment	11 (1.2%)	9 (1.9%)	52 (1.9%)	45 (2.4%)	16 (4.2%)	17 (4.4%)	68 (2.1%)
Renal Impairment ††	16 (1.7%)	19 (4.1%)	78 (2.8%)	81 (4.3%)	17 (4.5%)	33 (8.5%)	95 (3.0%)
Second primary malignancies excluding nonmelanoma skin cancer	27 (2.9%)	5 (1.1%)	66 (2.4%)	17 (3.2%)	12 (3.1%)	11 (2.8%)	78 (2.5%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

¶ Preferred term PRES: posterior reversible encephalopathy syndrome.

†† Non-prespecified treatment-emergent adverse events of interest.

‡‡ In addition to syncope, the preferred terms of presyncope, loss of consciousness, dizziness and postural dizziness were also evaluated.

Convulsion (seizure)

TEAEs of convulsion (seizure) were reported in 3 patients (0.3%) in the enzalutamide group and no patient in the placebo group. All 3 convulsions in the enzalutamide group were considered serious and drug-related, and occurred within 180 days of initiating study drug. One convulsion led to study drug discontinuation.

The incidence of any event of convulsion in the enzalutamide group of Study MDV3100-14 was similar to the enzalutamide group of the phase 3 studies and to the total enzalutamide group (0.3% vs. 0.4% and 0.4%). Overall the incidence of any event of seizure was low.

TEAEs of convulsion leading to death were not reported in any treatment group. Grade ≥ 3 events of convulsion were reported in 2 (0.2%) patients treated with enzalutamide in the Study MDV3100-14 and 8 (0.3%) patients treated with enzalutamide in phase 3 studies. No patient in the placebo group reported TEAEs of grade ≥ 3.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a rare neurological disorder that requires confirmation by brain imaging. PRES has been considered an ADR based on 2 post-marketing cases.

No cases of PRES were identified in Study MDV3100-14, the phase 3 studies, the total enzalutamide, placebo or bicalutamide groups.

The 'noninfectious encephalopathy/delirium' SMQ (narrow) was used to search for potential events of PRES. The following events were reported for 5 (0.5%) patients in the enzalutamide group of Study MDV3100-14 within the noninfectious encephalopathy/delirium SMQ: delirium (n = 3, 0.3%), encephalopathy (n = 1, 0.1%) and leukoencephalopathy (n = 1, 0.1%). The only patients in any study who had an event within the noninfectious encephalopathy/delirium SMQ leading to death were in the placebo group of the phase 3 studies (n = 3, 0.2%) and in bicalutamide group of the phase 2 studies (n = 1, 0.3%). No patients in any of the enzalutamide-treated groups had an event of potential PRES that led to death.

Cognitive and Memory Impairment

The incidence of TEAEs involving impaired cognition and memory (terms within the MedDRA high level group term 'mental impairment disorders') in the Study MDV3100-14 was higher in the enzalutamide group compared with the placebo group (5.2% vs. 1.9%).

The most frequent preferred terms reported were memory impairment (18 patients [1.9%] in the enzalutamide group vs. 4 patients [0.9%] in the placebo group) and disturbance in attention (15 patients [1.6%] in the enzalutamide group vs. 1 patient [0.2%] in the placebo group). A total of 28 patients (3.0%) in the enzalutamide group and 5 patients (1.1%) in the placebo group were considered to have a TEAE that was related to study drug. When events were adjusted for duration on treatment (events per 100 patient-years), the overall event rates were 3.8 in the enzalutamide group and 1.8 in the placebo group.

The incidence of any event of cognitive and memory impairment in the enzalutamide group of Study MDV3100-14 was similar to the enzalutamide group of the phase 3 studies and to the total enzalutamide group (5.2%, 4.9% and 4.9%). TEAEs of cognitive and memory impairment did not lead to any deaths for patients in any treatment group.

SAEs of cognitive and memory impairment and grade ≥ 3 cognitive and memory impairment events were low overall (≤ 1.0%) across the majority of all treatment groups. In the Study MDV3100-14 only 1 patient in the enzalutamide group and no patient in the placebo group experienced a Grade 3 or higher TEAEs of 'mental impairment' (the event was a Grade 3 cognitive disorder that led to study drug discontinuation). The incidence of TEAEs of cognitive and memory impairment leading to dose interruption in the enzalutamide group of Study MDV3100-14 was also low and similar to that in the enzalutamide group of the phase 3 studies (0.3% vs. 0.2%). The same is true for the TEAEs leading to dose reduction (0.2% vs. 0.1%) and TEAEs as the primary reason for discontinuation (0.2% vs. 0.3%).

Table 33. Treatment-emergent adverse events of cognitive and memory impairment

Preferred Term (MedDRA v16.1) Category n patients (%) Event Rate, (events)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Any event of cognitive and memory impairment	48 (5.2%)	9 (1.9%)	136 (4.9%)	29 (1.5%)	19 (5.0%)	5 (1.3%)	155 (4.9%)
Memory impairment Event rate (e)	18 (1.9%) 1.3 (19)	4 (0.9%) 0.8 (4)	49 (1.8%) 1.4 (51)	12 (0.6%) 0.9 (12)	7 (1.8%) 1.5 (7)	3 (0.8%) 0.9 (3)	56 (1.8%) 1.5 (58)
Disturbance in attention Event rate (e)	15 (1.6%) 1.1 (16)	1 (0.2%) 0.2 (1)	33 (1.2%) 1.0 (34)	5 (0.3%) 0.4 (5)	1 (0.3%) 0.2 (1)	1 (0.3%) 0.3 (1)	34 (1.1%) 0.9 (35)
Cognitive disorder Event rate (e)	7 (0.8%) 0.5 (7)	1 (0.2%) 0.2 (1)	23 (0.8%) 0.7 (23)	5 (0.3%) 0.4 (5)	1 (0.3%) 0.2 (1)	0	24 (0.8%) 0.6 (24)
Amnesia Event rate (e)	6 (0.6%) 0.4 (6)	1 (0.2%) 0.2 (1)	33 (1.2%) 0.9 (33)	5 (0.3%) 0.4 (5)	11 (2.9%) 2.6 (12)	0	44 (1.4%) 1.1 (45)
Dementia Alzheimer's type Event rate (e)	2 (0.2%) 0.1 (2)	1 (0.2%) 0.2 (1)	3 (0.1%) 0.1 (3)	1 (0.1%) 0.1 (1)	0	0	3 (0.1%) 0.1 (3)
Senile dementia Event rate (e)	2 (0.2%) 0.1 (2)	0	2 (0.1%) 0.1 (2)	0	0	0	2 (0.1%) 0.1 (2)
Dementia Event rate (e)	1 (0.1%) 0.1 (1)	0	3 (0.1%) 0.1 (3)	2 (0.1%) 0.2 (2)	1 (0.3%) 0.2 (1)	1 (0.3%) 0.3 (1)	4 (0.1%) 0.1 (4)
Vascular dementia Event rate (e)	1 (0.1%) 0.1 (1)	0	1 (0.0%) 0.0 (1)	0	0	0	1 (0.0%) 0.0 (1)
Mental impairment Event rate (e)	0	1 (0.2%) 0.2 (1)	1 (0.0%) 0.0 (1)	1 (0.1%) 0.1 (1)	0	0	1 (0.0%) 0.0 (1)
Any event of cognitive and memory impairment leading to death	0	0	0	0	0	0	0
Any serious event of cognitive and memory impairment	1 (0.1%)	0	1 (0.0%)	2 (0.1%)	1 (0.3%)	0	2 (0.1%)
Any grade ≥ 3 event of cognitive and memory impairment	1 (0.1%)	0	3 (0.1%)	2 (0.1%)	1 (0.3%)	0	4 (0.1%)
Any event of cognitive and memory impairment as the primary reason for treatment discontinuation	2 (0.2%)	0	7 (0.3%)	1 (0.1%)	2 (0.5%)	0	9 (0.3%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

In this table, "adverse events of cognitive and memory impairment" refers to all preferred terms in the MedDRA high level group 'mental impairment disorders'.

Time-adjusted rate per 100-patient-years (e) and number of events (n) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Selected Fatigue-related Events

Fatigue-related events were analyzed using the preferred terms of fatigue, asthenia, lethargy and malaise.

The incidence of fatigue-related TEAEs was higher in the enzalutamide group compared with the placebo group in Study MDV3100-14 (41.4% vs. 20.2%) as well as in the phase 3 studies (45.2% vs. 31.5%). The incidence of any event of fatigue in the enzalutamide group of Study MDV3100-14 was lower than the enzalutamide group of the phase 3 studies and the total enzalutamide group (41.4% vs. 45.2% and 44.3%).

The most common TEAE preferred terms contributing to fatigue-related events were fatigue and asthenia. The proportion of patients with the preferred term of fatigue was similar in the enzalutamide groups of Study MDV3100-14, the phase 3 studies and the total enzalutamide group (32.6%, 32.7% and 32.7%). In both Study MDV3100-14 and the phase 3 studies, the incidence of fatigue was higher in enzalutamide groups compared with their respective placebo groups (32.6% vs. 13.8% and 32.7% vs. 21.7%). When adjusted for the length of treatment, the event rate per 100 patient-years of fatigue was higher in the enzalutamide group as compared with the placebo group of Study MDV3100-14 (22.9 vs. 13.1) and lower in the enzalutamide group of the phase 3 studies compared with placebo (29.5 vs. 33.0).

Asthenia was the next most commonly reported preferred term. The incidence of asthenia in the enzalutamide groups of Study MDV3100-14, the phase 3 studies and the total enzalutamide group was 8.8%, 12.7% and 11.9%. In both Study MDV3100-14 and the phase 3 studies, the incidence of asthenia was higher in the enzalutamide group compared with the placebo group (8.8% vs. 6.0% and 12.7% vs. 9.0%). When adjusted for the length of treatment, the event rate per 100 patient-years of

asthenia was slightly higher in the enzalutamide group in Study MDV3100-14 compared with placebo (6.9 vs. 5.7) and lower in enzalutamide group of the phase 3 studies (12.4 vs. 14.2).

No deaths were associated with TEAEs of fatigue in any treatment group.

In general, the enzalutamide groups of Study MDV3100-14, the phase 3 studies and the total enzalutamide group had similar incidence of SAEs of fatigue (0.3%, 0.7% and 0.8%), grade ≥ 3 events of fatigue (4.0%, 5.0% and 4.9%) and any event of fatigue as the primary reason for discontinuation (1.9%, 1.1% and 1.3%).

Table 34. Selected fatigue-related treatment-emergent adverse events

Preferred Term (MedDRA v16.1) Category n patients (%) Event Rate, (events)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	Enzalutamide§ (n = 3179)
Any event of fatigue	385 (41.4%)	94 (20.2%)	1265 (45.2%)	597 (31.5%)	144 (37.9%)	110 (28.4%)	1409 (44.3%)
Fatigue Event rate (e)	303 (32.6%) 22.9 (329)	64 (13.8%) 13.1 (67)	914 (32.7%) 29.5 (1042)	412 (21.7%) 33.0 (436)	125 (32.9%) 29.1 (136)	94 (24.3%) 30.4 (99)	1039 (32.7%) 29.5 (1178)
Asthenia Event rate (e)	82 (8.8%) 6.9 (99)	28 (6.0%) 5.7 (29)	356 (12.7%) 12.4 (438)	171 (9.0%) 14.2 (188)	22 (5.8%) 5.8 (27)	13 (3.4%) 4.0 (13)	378 (11.9%) 11.6 (465)
Malaise Event rate (e)	13 (1.4%) 1.0 (15)	3 (0.6%) 0.6 (3)	31 (1.1%) 1.2 (41)	12 (0.6%) 0.9 (12)	0	5 (1.3%) 1.5 (5)	31 (1.0%) 1.0 (41)
Lethargy Event rate (e)	14 (1.5%) 1.0 (15)	2 (0.4%) 0.4 (2)	50 (1.8%) 1.5 (52)	32 (1.7%) 2.8 (37)	8 (2.1%) 1.9 (9)	5 (1.3%) 1.5 (5)	58 (1.8%) 1.5 (61)
Any event of fatigue leading to death	0	0	0	0	0	0	0
Any serious event of fatigue	3 (0.3%)	1 (0.2%)	20 (0.7%)	12 (0.6%)	6 (1.6%)	3 (0.8%)	26 (0.8%)
Any grade ≥ 3 event of fatigue	37 (4.0%)	4 (0.9%)	141 (5.0%)	68 (3.6%)	15 (3.9%)	9 (2.3%)	156 (4.9%)
Any event of fatigue as the primary reason for treatment discontinuation	18 (1.9%)	1 (0.2%)	30 (1.1%)	18 (0.9%)	10 (2.6%)	6 (1.6%)	40 (1.3%)

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

In this table, "adverse events of fatigue" refers to the preferred terms of fatigue, asthenia, lethargy and malaise.

Time-adjusted rate per 100 patient-years (e) and number of events (n) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment emergent period for each treatment group times 100. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Neutrophil Count Decreased

Overall, the TEAE incidence of any event of neutrophil count decreased (involving neutropenia, low neutrophil count and low white blood cell count) was higher in the enzalutamide group compared with the placebo group of both Study MDV3100-14 (0.9% vs.. 0.2%) and the phase 3 studies (1.4% vs.. 0.6%). The incidence of any event of neutrophil count decreased in the enzalutamide group of Study MDV3100-14 was lower than the enzalutamide group of the phase 3 studies and the total enzalutamide group (0.9% vs. 1.4% and 1.4%).

The most frequent TEAEs of neutrophil count decreased were neutropenia and neutrophil count decreased. In both Study MDV3100-14 and the phase 3 studies, the incidence of neutropenia was higher in the enzalutamide group compared with placebo group (0.6% vs.. 0.2% and 0.8% vs.. 0.3%). The incidence of neutropenia in the enzalutamide group of Study MDV3100-14 was similar compared with the phase studies 3 and the total enzalutamide group (0.6%, 0.8% and 0.8%).

Neutrophil count decreased was the next most common preferred term. The incidence of neutrophil count decreased events was low and comparable in the enzalutamide groups of Study MDV3100-14, the phase 3 studies and the total enzalutamide group (0.2%, 0.4% and 0.4%). In both Study MDV3100-14 and the phase 3 studies, the incidence of neutrophil count decreased was slightly higher in enzalutamide group compared with placebo group (0.2% vs. 0 and 0.4% vs. 0.2%).

There were no patients who had any TEAE of neutrophil count decreased leading to death in any of the treatment groups across the studies.

In general, Study MDV3100-14, the phase 3 studies and the total enzalutamide group had low and similar incidence of SAEs of neutrophil count decreased (0, 0.1% and 0.1%), grade ≥ 3 events of neutrophil count decreased (0.5%, 0.8% and 0.7%) and neutrophil count decreased events as the primary reason for discontinuation (0, 0.1% and 0.1%).

Fall

Overall, the incidence of TEAEs of fall was higher in the enzalutamide group compared with the placebo group of both Study MDV3100-14 (11.4% vs. 4.1%) and the phase 3 studies (9.1% vs. 3.6%). The incidence of fall in the enzalutamide group of Study MDV3100-14 was higher than in the enzalutamide group of the phase 3 studies and the total enzalutamide group (11.4%, 9.1% and 9.3%). When adjusted for treatment duration, the event rate per 100 patient-years of fall was higher in the enzalutamide group of Study MDV3100-14 compared with the placebo group (9.5 vs. 4.1). The event rate of fall in the enzalutamide group of Study MDV3100-14 was similar to the event rates in the enzalutamide group of the phase 3 studies and the total enzalutamide group (9.5, 9.1 and 9.4).

In general, the incidence of SAEs of fall was low and similar among the enzalutamide groups of Study MDV3100-14, the phase 3 studies and the total enzalutamide group (0.8%, 0.6% and 0.6%), as well as the incidence of grade ≥ 3 events (1.3%, 1.0% and 1.0%). There were no events of fall as the primary reason for discontinuation in Study MDV3100-14 or in the phase 3 studies. No deaths were associated with TEAEs of fall in any treatment group across the studies.

The incidence of fall increased with age. In the enzalutamide group of Study MDV3100-14 the proportion of patients with an event of fall was 7.4% in patients < 75 years and 15.8% in patients ≥ 75 years. A similar pattern was observed in the phase 3 studies and the total enzalutamide group.

An exploratory analysis of TEAEs of syncope-related events (syncope, presyncope, loss of consciousness, dizziness and postural dizziness) reported within 1 day prior to TEAEs of fall was performed to evaluate the possible association of syncope-related events with fall. Among patients with fall, a similar proportion in the enzalutamide and placebo groups had 1 or more syncope-related events within 1 day prior to a fall (5.7% [6/106] vs. 5.3% [1/19] in Study MDV3100-14; 3.5% [9/256] vs. 2.9% [2/69] in the phase 3 studies). Among the 106 enzalutamide-treated patients with a TEAE of fall in Study MDV3100-14, 4 patients (3.8%) had dizziness, 1 patient had syncope (0.9%) and 1 patient had a presyncope event (0.9%) within 1 day prior to the TEAE of fall. Among the 256 enzalutamide-treated patients with a TEAE of fall in phase 3 studies, 6 patients (2.3%) reported dizziness, 2 patients had syncope (0.8%) and 1 patient had a presyncope event (0.4%) within 1 day prior to the TEAE of fall.

There were no enzalutamide-treated patients with postural dizziness or loss of consciousness reported within 1 day prior to a TEAE of fall in Study MDV3100-14, the phase 3 studies or the total enzalutamide group.

Fractures

The events of fractures have been previously reported in patients treated with enzalutamide. In the Study MDV3100-14 a higher incidence of fractures was reported in the enzalutamide group compared with the placebo group (11.2% vs. 5.6%). The most common types of fracture reported among the enzalutamide groups of Study MDV3100-14, the phase 3 studies and total enzalutamide group were rib fracture (4.2%, 2.4% and 2.5%), followed by spinal compression fracture (1.8%, 1.2% and 1.2%), femur fracture (0.5%, 0.4% and 0.3%) and upper limb fracture (0.5%, 0.3% and 0.3%).

When adjusted for treatment duration, the event rates per 100 patient-years of fracture was higher in the enzalutamide group of Study MDV3100-14 (9.5 vs. 5.1) and in the enzalutamide groups of the phase 3 studies (8.1 vs. 4.8) compared to placebo.

In general, the incidences of SAEs of fractures were low and similar among the enzalutamide groups of Study MDV3100-14, the phase 3 studies and the total enzalutamide group (2.8%, 2.9% and 3.0%), as were grade ≥ 3 events of fracture (2.4%, 2.6% and 2.7%) and any event of fracture as the primary reason for discontinuation (0.2%, 0.1% and 0.1 %). One event of fracture, occurring in an enzalutamide-treated patient in Study MDV3100-14, led to a fatal outcome due to complications of fracture.

The incidence of fractures increased with the length of treatment duration, with the majority of fractures reported after 180 days of study treatment.

Syncope, Presyncope, Loss of Consciousness, Dizziness and Postural Dizziness

SAEs, grade ≥ 3 TEAEs and TEAEs as the primary reason for discontinuation were uncommon for events of syncope, presyncope, loss of consciousness, dizziness and postural dizziness in Study MDV3100-14 and in the phase 3 studies.

The incidence and/or event rates of syncope, loss of consciousness and postural dizziness were similar between the enzalutamide and placebo groups in Study MDV3100-14 and in the phase 3 studies.

The incidence of presyncope was low, but higher in the enzalutamide group compared with the placebo in Study MDV3100-14 (1.0% vs. 0) and in the phase 3 studies (1.0% vs. 0.2%).

In Study MDV3100-14, the incidence of dizziness was higher in the enzalutamide group compared with the placebo group (9.8% vs. 4.3%) with event rates of 7.2 vs. 4.9. In the phase 3 studies, the incidence of dizziness was also higher in the enzalutamide group (8.6% vs. 5.4%), however event rates adjusted for duration of treatment were lower in the enzalutamide group (7.7 vs. 8.5).

No enzalutamide-treated patients died due to a TEAE of syncope, presyncope, loss of consciousness, dizziness or postural dizziness.

An exploratory analysis of TEAEs of syncope, presyncope, loss of consciousness, dizziness and postural dizziness reported within 1 day prior to fall TEAEs does not suggest an association of these events with falls among enzalutamide-treated patients.

Hypertension

Hypertension is a known adverse event related to enzalutamide treatment and already described in previous studies. In the Study MDV3100-14 the incidence hypertension was higher in the enzalutamide group compared with the placebo group (12.3% vs. 5.4%) as it was in the phase 3 studies (11.3% vs. 4.3%).

When adjusted for treatment duration, the event rate for hypertension was higher in enzalutamide groups compared with the placebo group in both Study MDV3100-14 (8.4 vs. 5.1) and phase 3 studies (9.4 vs. 5.7). The incidence of any event of hypertension was comparable in the enzalutamide group of Study MDV3100-14, the phase 3 studies and the total enzalutamide group (12.3%, 11.3% and 11.7%).

TEAEs of hypertension leading to death were not reported in any treatment group. In Study MDV3100-14, 1 enzalutamide-treated patient experienced an event of grade 4 hypertension.

Overall the incidence of SAEs of hypertension was low and similar in the enzalutamide groups of Study MDV3100-14, the phase 3 studies and in the total enzalutamide group (0.3%, 0.3% and 0.4%). Similar trends were reported for grade ≥ 3 TEAEs (4.6%, 4.8% and 5.1%). The incidence of TEAEs of hypertension as the primary reason for study drug discontinuation was low for the enzalutamide groups in Study MDV3100-14 and the phase 3 studies (0.1%). TEAEs of hypertension leading to dose

interruption or dose reduction were more frequent in the enzalutamide groups in Study MDV3100-14 and the phase 3 studies, compared with their respective placebo group.

The incidence of hypertension was similar in enzalutamide-treated patients with and without history of hypertension and were higher compared with those in the placebo groups (12.1% vs.. 5.0% in patients with prior history of hypertension and 11.7% vs. 5.6% in patients without hypertension history).

Overall, the incidence of events of hypertension in Study MDV3100-14 was similar to the incidence observed in enzalutamide-treated patients in prior studies with less than 1.0% events being reported as
SAEs, approximately 5% of patients experienced grade ≥ 3 events and permanent discontinuations from study treatment due to hypertension were rare.

Selected Cardiovascular Events

In Study MDV3100-14, 5.2% of patients in the enzalutamide group and 2.8% of patients in the placebo group experienced a major adverse cardiovascular event (MACE). MACE included a composite of cardiovascular and cerebrovascular TEAEs based on narrow SMQs of 'myocardial infarction', 'cardiac failure', haemorrhagic cerebrovascular conditions', and 'ischaemic cerebrovascular conditions'.
The MACE rates (events per 100 patient-years) were 4.1 vs. 2.9 in the enzalutamide and placebo groups.

Grade 3 or higher MACE occurred in 34 of 48 patients (70.8%) in the enzalutamide group and 8 of 13 patients (61.5%) in the placebo group. The majority of Grade 3 or higher MACE occurred after 365 days. In both treatment groups, the majority of MACE was assessed as serious (36 of 48 patients in the enzalutamide group and 8 of 13 patients in the placebo group).

In Study MDV3100-14, MACE incidence was similar for the enzalutamide group compared with the placebo group in days 1 to 30 (0.2% vs. 0) and days 181 to 365 (1.1% vs. 1.1%), but was higher in the enzalutamide group compared with the placebo group for days 31 to 180 (1.2% vs. 0.4%) and > 365 days (4.5% vs. 3.8%). In the phase 3 studies, MACE incidence was similar for the enzalutamide group compared with the placebo group across all discrete time periods (0.3% vs. 0.2% for days 1 to 30; 1.4% vs. 1.2% for days 31 to 180; 1.6% vs. 1.3% for days 181 to 365 and 3.3% vs. 3.2% for > 365 days).

To further characterize a treatment group imbalance in MACE observed in Study MDV3100-14, an additional composite, designated as Antiplatelet Trialists' Collaboration (APTC) MACE (vascular death, nonfatal MI, and nonfatal cerebrovascular accident) was included.

In Study MDV3100-14, 4.2% of patients in the enzalutamide group and 2.2% of patients in the placebo group experienced an APTC MACE. The APTC MACE rates (events per 100 patient-years) were 3.3 vs. 2.3 in the enzalutamide and placebo groups.

In Study MDV3100-14, the enzalutamide group had APTC MACE incidence of 0.2% in days 1 to 30 compared with no events in the placebo group. The APTC MACE incidence was higher in the enzalutamide group compared with the placebo group between days 31 to 180 (0.7% vs. 0.2%), days 181 to 365 (1.3% vs. 0.6%) and > 365 days (3.7% vs. 3.3%). In the phase 3 studies (Study MDV3100-14 pooled with the other 3 randomized, placebo-controlled, double-blind phase 3 studies), APTC MACE incidence was similar for the enzalutamide group compared with the placebo group across all discrete time periods (0.2% vs. 0.2% for days 1 to 30; 1.0% vs. 1.1% for days 31 to 180; 1.2% vs. 1.0% for days 181 to 365; 2.7% vs. 2.5% for > 365 days).

Table 35. Selected Treatment-Emergent Cardiovascular Events –MACE

Parameter (MedDRA v16.1) Category n patients (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Incidence, n (%) **Event rate, rate (number of events)**							
Selected cardiovascular events (MACE) (total) Event rate (e)	48 (5.2%) 4.1 (59)	13 (2.8%) 2.9 (15)	126 (4.5%) 4.2 (147)	50 (2.6%) 4.5 (59)	24 (6.3%) 6.4 (30)	11 (2.8%) 4.0 (13)	150 (4.7%) 4.4 (177)
Myocardial infarction SMQ Event rate (e)	18 (1.9%) 1.5 (22)	5 (1.1%) 1.2 (6)	36 (1.3%) 1.1 (40)	13 (0.7%) 1.1 (14)	8 (2.1%) 1.7 (8)	1 (0.3%) 0.3 (1)	44 (1.4%) 1.2 (48)
Haemorrhagic cerebrovascular conditions SMQ Event rate (e)	6 (0.6%) 0.4 (6)	1 (0.2%) 0.2 (1)	23 (0.8%) 0.7 (23)	9 (0.5%) 0.8 (10)	3 (0.8%) 0.6 (3)	0	26 (0.8%) 0.7 (26)
Ischaemic cerebrovascular conditions SMQ Event rate (e)	17 (1.8%) 1.3 (19)	4 (0.9%) 0.8 (4)	42 (1.5%) 1.3 (46)	19 (1.0%) 1.4 (19)	10 (2.6%) 2.4 (11)	3 (0.8%) 0.9 (3)	52 (1.6%) 1.4 (57)
Cardiac failure SMQ Event rate (e)	15 (1.6%) 1.1 (16)	5 (1.1%) 1.0 (5)	44 (1.6%) 1.4 (50)	17 (0.9%) 1.4 (19)	9 (2.4%) 2.4 (11)	8 (2.1%) 2.8 (9)	53 (1.7%) 1.5 (61)

Table 36. Selected Treatment-Emergent Cardiovascular Events –APTC MACE

Parameter (MedDRA v16.1) Category n patients (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Incidence, n (%) **Event rate, rate (number of events)**							
APTC MACE (total) Event rate (e)	39 (4.2%) 3.3 (47)	10 (2.2%) 2.3 (12)	100 (3.6%) 3.1 (110)	43 (2.3%) 3.6 (47)	19 (5.0%) 4.5 (21)	4 (1.0%) 1.2 (4)	119 (3.7%) 3.3 (131)
Nonfatal myocardial infarction Event rate (e)	12 (1.3%) 1.1 (16)	5 (1.1%) 1.2 (6)	27 (1.0%) 0.9 (31)	12 (0.6%) 1.0 (13)	6 (1.6%) 1.3 (6)	1 (0.3%) 0.3 (1)	33 (1.0%) 0.9 (37)
Nonfatal cerebrovascular accidents Event rate (e)	18 (1.9%) 1.4 (20)	4 (0.9%) 0.8 (4)	47 (1.7%) 1.4 (51)	22 (1.2%) 1.8 (24)	10 (2.6%) 2.4 (11)	3 (0.8%) 0.9 (3)	57 (1.8%) 1.6 (62)
Vascular deaths†† Event rate (e)	12 (1.3%) 0.8 (12)	2 (0.4%) 0.4 (2)	29 (1.0%) 0.8 (29)	10 (0.5%) 0.8 (10)	4 (1.1%) 0.9 (4)	0	33 (1.0%) 0.8 (33)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Nonfatal myocardial infarction was defined as nonfatal TEAEs in the narrow SMQ of myocardial infarction. Nonfatal cerebrovascular accidents were defined as nonfatal TEAEs in either narrow SMQ of haemorrhagic or ischaemic cerebrovascular conditions. Vascular deaths were defined as fatal TEAEs in the SOC of cardiac disorders, fatal cerebrovascular accidents and fatal TEAE in the broad SMQ of torsade de pointes/QT prolongation.

Time-adjusted rate per 100-patient-years and number of events (e) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

APTC: Antiplatelet Trialists' Collaboration; MACE: major cardiovascular events; NR: not reached; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event

Second primary malignancies

Overall, the incidence of second primary malignancies was higher in the enzalutamide group of Study MDV3100-14 compared with the placebo group (2.9% vs. 1.1%). In the phase 3 studies, the incidence of any second primary malignancy was also higher in the enzalutamide group compared with the placebo group (2.4% vs. 0.9%). The incidence of any second primary malignancy in the enzalutamide group of Study MDV3100-14 was similar to the enzalutamide group of the phase 3 studies and to the total enzalutamide group (2.9% vs. 2.4% and 2.5%).

After adjustment for length of treatment duration, second primary malignancy event rates per 100 patient-years were higher for the enzalutamide-treated patients compared with the placebo groups in Study MDV3100-14 (2.1 vs. 1.0) and the phase 3 studies (2.0 vs. 1.4).

The most common second primary malignancies in the enzalutamide group of Study MDV3100-14 were adenocarcinoma of the colon (0.5%), chronic lymphocytic leukaemia (0.2%), bladder cancer (0.2%) and bladder transitional cell carcinoma (0.2%). All other reported second primary malignancies in the enzalutamide group had only 1 reported TEAE (by preferred term).

The proportion of patients in the enzalutamide group of Study MDV3100-14 with a second primary malignancy that lead to death (0.5%) was slightly higher than in placebo group (0.2%) and the same pattern was observed in the phase 3 studies (0.3% vs. 0.1%).

Serious adverse event / deaths / other significant events

Serious adverse events

Overall, the incidence of treatment-emergent SAEs reported in the MDV3100-14 enzalutamide group was higher than the incidence for the MDV3100-14 placebo group (24.3% vs. 18.3%). Of these, serious TEAEs considered related to study drug occurred in 3.4% of patients in the enzalutamide group and 2.6% in the placebo group.

The proportion of study-drug-related treatment emergent SAEs in the MDV3100-14 enzalutamide group was similar to the enzalutamide and placebo groups of the phase 3 studies (3.3% and 3.2%) and the total enzalutamide group (3.6%).

Serious TEAEs reported in at least 1% of patients in either treatment group included hematuria and pneumonia in the enzalutamide group and hematuria, urinary retention, renal failure acute and urinary tract infection in the placebo group. In Study MDV3100-14, the only SAE in ≥ 1% patients that was ≥ 0.5% higher in the enzalutamide group compared with placebo group was pneumonia (1.0% vs. 0.2%). Conversely, SAE reported in ≥ 1% of patients in either treatment group that was ≥ 0.5% higher in the placebo group of Study MDV3100-14 compared with the enzalutamide group were urinary retention (1.7% vs. 0.8%), acute renal failure (0.4% vs. 1.5%) and urinary tract infection (0.5% vs. 1.3%).

In both treatment groups, a high proportion of patients with serious TEAEs occurred in the SOC Cardiac disorders (4.8% in the enzalutamide group vs. 2.4% in the placebo group).

When adjusted for treatment duration, the event rates for these treatment-emergent SAEs showed a pattern of reversal of the differences in incidences between the phase 3 enzalutamide and placebo groups for pneumonia (1.1 enzalutamide vs. 1.1 placebo), anemia (1.4 vs. 2.4), general physical health deterioration (1.0 vs. 1.4), spinal cord compression (2.5 vs. 3.2) and metastatic pain (1.1 vs. 1.7).

Table 37. Treatment-Emergent Serious Adverse Events (TESAEs) Reported in at least 0.5% of patients in either treatment group in the Study MDV3100-14 by Preferred Term (Safety population)

	Enzalutamide (N = 930)	Placebo (N = 465)
Number of patients reporting at least 1 serious TEAE	226 (24.3%)	85 (18.3%)
Haematuria	20 (2.2%)	11 (2.4%)
Urinary retention	7 (0.8%)	8 (1.7%)
Renal failure acute	4 (0.4%)	7 (1.5%)
Urinary tract infection	5 (0.5%)	6 (1.3%)
Pneumonia	9 (1.0%)	1 (0.2%)
Atrial fibrillation	6 (0.6%)	3 (0.6%)
Fall	7 (0.8%)	2 (0.4%)
Acute myocardial infarction	6 (0.6%)	2 (0.4%)
Adenocarcinoma of colon	5 (0.5%)	2 (0.4%)
Anaemia	5 (0.5%)	1 (0.2%)
Cardiac failure	6 (0.6%)	0 (0.0%)
Chest pain	5 (0.5%)	1 (0.2%)
Myocardial infarction	6 (0.6%)	0 (0.0%)
Pulmonary embolism	3 (0.3%)	3 (0.6%)
Coronary artery disease	5 (0.5%)	0 (0.0%)
Osteoarthritis	2 (0.2%)	3 (0.6%)
Back pain	1 (0.1%)	3 (0.6%)
Hydronephrosis	1 (0.1%)	3 (0.6%)
Urethral stenosis	1 (0.1%)	3 (0.6%)
Obstructive uropathy	0 (0.0%)	3 (0.6%)

Source: Table 14.3.2.1.2 and Table 14.3.2.1.1.
Note: Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).
Patients with multiple events for a given preferred term and overall, were counted once only for the preferred term and overall, respectively.
Events were sorted by decreasing frequency of preferred term.
MedDRA Version 16.1.
CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; NCI=National Cancer Institute; TEAE=treatment-emergent adverse event

Table 38. Treatment-Emergent Serious Adverse Events (TESAEs) experienced by ≥ 1% of patients in the phase 3 enzalutamide or placebo groups

Preferred Term (MedDRA v16.1) Category n patients (%) Event Rate, (events)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Haematuria	20 (2.2%)	11 (2.4%)	44 (1.6%)	33 (1.7%)	6 (1.6%)	5 (1.3%)	50 (1.6%)
Event rate (e)	1.7 (24)	3.1 (16)	1.7 (61)	2.9 (38)	1.3 (6)	2.1 (7)	1.7 (67)
Pneumonia	9 (1.0%)	1 (0.2%)	35 (1.3%)	14 (0.7%)	7 (1.8%)	4 (1.0%)	42 (1.3%)
Event rate (e)	0.6 (9)	0.2 (1)	1.1 (38)	1.1 (14)	1.5 (7)	1.2 (4)	1.1 (45)
Urinary retention	7 (0.8%)	8 (1.7%)	24 (0.9%)	30 (1.6%)	1 (0.3%)	4 (1.0%)	25 (0.8%)
Event rate (e)	0.6 (8)	1.6 (8)	0.9 (30)	2.3 (31)	0.2 (1)	1.2 (4)	0.8 (31)
Anaemia	5 (0.5%)	1 (0.2%)	42 (1.5%)	26 (1.4%)	6 (1.6%)	4 (1.0%)	48 (1.5%)
Event rate (e)	0.3 (5)	0.2 (1)	1.4 (50)	2.4 (32)	1.5 (7)	1.2 (4)	1.4 (57)
General physical health deterioration	2 (0.2%)	0	35 (1.3%)	18 (0.9%)	2 (0.5%)	1 (0.3%)	37 (1.2%)
Event rate (e)	0.1 (2)		1.0 (35)	1.4 (19)	0.4 (2)	0.3 (1)	0.9 (37)
Spinal cord compression	2 (0.2%)	1 (0.2%)	84 (3.0%)	41 (2.2%)	1 (0.3%)	1 (0.3%)	85 (2.7%)
Event rate (e)	0.1 (2)	0.2 (1)	2.5 (87)	3.2 (42)	0.2 (1)	0.3 (1)	2.2 (88)
Metastatic pain	0	0	30 (1.1%)	20 (1.1%)	2 (0.5%)	2 (0.5%)	32 (1.0%)
Event rate (e)			1.0 (37)	1.7 (23)	0.4 (2)	0.9 (3)	1.0 (39)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of subjects (n) reporting and percentage of subjects (%) are shown. The preferred terms were coded by MedDRA v 16.1. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event at the worst grade. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in MDV3100-14.

Time-adjusted rate per 100-patient-years and number of events (e) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Deaths

A total of 103 enzalutamide-treated patients (11.0%) and 62 placebo-treated patients (13.2%) died as of the data cutoff date of study MDV3100-14. Disease progression was the most common cause of death reported on the end of study CRF (5.5% of enzalutamide-treated patients and 9.6% of placebo-treated patients), followed by death due to other causes (5.3% vs. 3.4%) which included TEAEs leading to death, and deaths due to unknown causes (0.3% vs. 0.2%).

One patient (0.1%) in the enzalutamide group died within 30 days of initiation of study drug (an acute myocardial infarction 21 days after initiating study drug), and a total of 28 patients (3.0%) in the enzalutamide group and 2 patients (0.4%) in the placebo group died within 30 days of discontinuation of study drug.

TEAEs leading to death in at least 2 patients in the total enzalutamide group are presented in Table 37. Summary of all deaths. The proportion of patients with TEAEs leading to death was higher in the enzalutamide group of Study MDV3100-14 than in the placebo group (3.4% vs. 0.6%). Of the 32 patients who had TEAEs leading to death in the enzalutamide group, 2 patients had TEAES that were considered by the investigator to be related to the study drug (general physical health deterioration and duodenal ulcer hemorrhage).

The majority of deaths (19 [2.4%] in the enzalutamide group vs. 2 [0.7%] patients in the placebo group) occurred > 365 days after initiating study drug. The most frequently reported preferred terms leading to death were myocardial infarction (MI) (0.4%), general physical health deterioration (0.2%) and acute MI (0.2%).

In the Study MDV3100-14 the system organ classes with the highest percentage of reported TEAEs leading to deaths (≥0.5% in either treatment group) were Cardiac disorders (1.0% enzalutamide vs. 0.4% placebo). In the total enzalutamide group TEAEs leading to death was reported under the SOC of general disorders and administration site conditions followed by cardiovascular disorders. The most frequently reported preferred terms included general physical health deterioration (0.6%), death (0.2%), disease progression (0.2%), acute MI (0.2%), cardiac failure (0.2%) and pneumonia (0.2%).

When adjusted for treatment duration, the event rates for these TEAEs leading to death in the total enzalutamide group were low: general physical health deterioration (0.5), death (0.2), disease progression (0.2), acute MI (0.1), cardiac failure (0.1) and pneumonia (0.1).

Table 39. Summary of all deaths

Summary of Deaths, n (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§ (n = 3179)
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	
Total number of deaths	102 (11.0%)	62 (13.3%)	982 (35.1%)	759 (40.0%)	17 (4.5%)	13 (3.4%)	999 (31.4%)
Cause of death							
Disease progression	50 (5.4%)	45 (9.7%)	786 (28.1%)	631 (33.2%)	3 (0.8%)	1 (0.3%)	789 (24.8%)
Other¶	49 (5.3%)	16 (3.4%)	139 (5.0%)	96 (5.1%)	13 (3.4%)	8 (2.1%)	152 (4.8%)
Unknown††	3 (0.3%)	1 (0.2%)	57 (2.0%)	30 (1.6%)	0	0	57 (1.8%)
Not reported	0	0	0	0	1 (0.3%)	4 (1.0%)	1 (0.0%)
Missing	0	0	0	2 (0.1%)	0	0	0
Deaths within 30 days after the first dose date of study drug	1 (0.1%)	0	4 (0.1%)	4 (0.2%)	1 (0.3%)	0	5 (0.2%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

¶ Known causes other than prostate cancer.

†† Unknown etiologies or cause was not available to the investigator.

Table 40. Treatment-emergent adverse events resulting in death by preferred term in at least 2 patients in the total enzalutamide

Preferred Term (MedDRA v16.1), n patients (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§ (n = 3179)
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	
Patients with ≥ 1 TEAE resulting in death, overall n (%)	32 (3.4%)	3 (0.6%)	107 (3.8%)	56 (3.0%)	15 (3.9%)	9 (2.3%)	122 (3.8%)
Myocardial infarction	4 (0.4%)	0	4 (0.1%)	1 (0.1%)	1 (0.3%)	0	5 (0.2%)
Acute myocardial infarction	2 (0.2%)	0	5 (0.2%)	0	1 (0.3%)	0	6 (0.2%)
General physical health deterioration	2 (0.2%)	0	18 (0.6%)	9 (0.5%)	1 (0.3%)	1 (0.3%)	19 (0.6%)
Cardiac failure	1 (0.1%)	0	5 (0.2%)	0	0	0	5 (0.2%)
Cardio-respiratory arrest	1 (0.1%)	0	1 (0.0%)	0	1 (0.3%)	0	2 (0.1%)
Cerebrovascular accident	1 (0.1%)	0	4 (0.1%)	0	0	0	4 (0.1%)
Death	1 (0.1%)	0	7 (0.3%)	3 (0.2%)	0	0	7 (0.2%)
Disease progression	1 (0.1%)	0	7 (0.3%)	6 (0.3%)	0	1 (0.3%)	7 (0.2%)
Hepatic failure	1 (0.1%)	0	2 (0.1%)	0	1 (0.3%)	0	3 (0.1%)
Metastases to liver	1 (0.1%)	0	1 (0.0%)	0	1 (0.3%)	0	2 (0.1%)
Pneumonia	1 (0.1%)	0	5 (0.2%)	1 (0.1%)	1 (0.3%)	0	6 (0.2%)
Pneumonia aspiration	1 (0.1%)	0	1 (0.0%)	0	1 (0.3%)	1 (0.3%)	2 (0.1%)
Septic shock	1 (0.1%)	0	3 (0.1%)	2 (0.1%)	0	1 (0.3%)	3 (0.1%)
Cachexia	0	0	2 (0.1%)	1 (0.1%)	0	0	2 (0.1%)
Cardiac arrest	0	1 (0.2%)	2 (0.1%)	2 (0.1%)	0	0	2 (0.1%)
Cardiopulmonary failure	0	0	2 (0.1%)	0	0	0	2 (0.1%)
Pulmonary embolism	0	0	2 (0.1%)	1 (0.1%)	0	0	2 (0.1%)
Sepsis	0	0	2 (0.1%)	0	0	0	2 (0.1%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Patients with multiple events for a given preferred term were counted only once for each preferred term per time interval.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Laboratory findings

Haematology

Overall, the incidence of grade 3 and 4 post-baseline hematology toxicities occurring in enzalutamide-treated patients in Study MDV3100-14 was low (≤ 0.6% of patients across all parameters).

In the Study MDV3100-14, the proportions of patients with low lymphocyte count and low hemoglobin in the enzalutamide group were similar to those reported in the placebo group (0.4% vs. 0.2% for low lymphocytes and 0.6% vs. 0.4% for low hemoglobin, respectively). This may in part be indicative of the nonmetastatic disease patient population in Study MDV3100-14. The proportion of patients with these hematology toxicities was lower in the enzalutamide group of Study MDV3100-14 than in the enzalutamide groups of the phase 3 studies (3.6% and 2.2%) and in the total enzalutamide groups (3.6% and 2.2%). In the enzalutamide group of the phase 3 studies, the proportion of patients with low lymphocyte count and low hemoglobin was comparable to the proportion of patients with events in their respective placebo group. However, the proportion of patients with these hematology toxicities was lower in the placebo group of Study MDV3100-14 than the proportion of patients with events in the placebo group of the phase 3 studies (0.2% vs. 3.6% for low lymphocytes and 0.4% vs. 2.0% for low hemoglobin).

Tabla 41. Hematology Results: Summary of Grade 3 and 4 Post-baseline Laboratory Toxicities

Parameter (Unit) [Direction of Criteria], n (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	(n = 3179)
Hemoglobin (g/L) [low]	6 (0.6%)	2 (0.4%)	62 (2.2%)	38 (2.0%)	7 (1.8%)	6 (1.6%)	69 (2.2%)
Hemoglobin (g/L) [high]	0	0	2 (0.1%)	1 (0.1%)	0	0	2 (0.1%)
Leukocytes (10^9/L) [low]	1 (0.1%)	0	12 (0.4%)	3 (0.2%)	1 (0.3%)	2 (0.5%)	13 (0.4%)
Lymphocytes (10^6/L) [high]	0	0	0	0	0	0	0
Lymphocytes (10^6/L) [low]	4 (0.4%)	1 (0.2%)	102 (3.6%)	69 (3.6%)	12 (3.2%)	9 (2.3%)	114 (3.6%)
Neutrophils (10^6/L) [low]	5 (0.5%)	1 (0.2%)	23 (0.8%)	7 (0.4%)	2 (0.5%)	2 (0.5%)	25 (0.8%)
Platelets (10^9/L) [low]	1 (0.1%)	0	6 (0.2%)	8 (0.4%)	2 (0.5%)	1 (0.3%)	8 (0.3%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Number of subjects (n) and percentage of subjects (%) are shown.

Grade 3 and 4 toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.

Patients were generally counted only once for each parameter. However, for parameters with both high and low criteria, patients are counted only once for each criterion (high or low), so a single patient can count towards both high and low criteria if the patient has laboratory values meeting each criterion. Summaries are based on all test results collected in the treatment-emergent period.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Source: [Module 5.3.5.3 ISS/SCS Table 14.3.4.1.1]

Chemistry

The most common grade 3 and 4 postbaseline chemistry laboratory toxicity in Study MDV3100-14 was high glucose. The proportion of patients with high glucose in the enzalutamide group of Study MDV3100-14 was higher than the MDV3100-14 placebo group (2.9% vs. 1.3%). The proportion of patients with high glucose in the enzalutamide group of the phase 3 studies was higher compared with the phase 3 placebo group (2.9% vs. 2.3%).

The proportion of patients with high glucose in the enzalutamide group of Study MDV3100-14 and the phase 3 studies was the same (2.9% each) but was lower than the proportion of patients with high glucose in the total enzalutamide groups (3.5%).

With the exception of high alkaline phosphatase (ALP) and low sodium, the proportion of all other grade 3 and 4 postbaseline laboratories toxicities occurred in < 2% of patients in any treatment group.

There were no patients with high ALP in the Study MDV3100-14 enzalutamide group, compared with 0.2% in the placebo group and 5.6% in the phase 3 studies enzalutamide group.

Table 42. Chemistry results: Summary of Grade 3 and 4 postbaseline laboratory toxicities

Parameter (Unit) [Direction of Criteria], n (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	Enzalutamide§ (n = 3179)
Alanine aminotransferase (U/L) [high]	2 (0.2%)	0	6 (0.2%)	2 (0.1%)	4 (1.1%)	3 (0.8%)	10 (0.3%)
Albumin (g/L) [low]	0	0	10 (0.4%)	5 (0.3%)	0	0	10 (0.3%)
Alkaline phosphatase (U/L) [high]	0	1 (0.2%)	158 (5.6%)	160 (8.4%)	11 (2.9%)	20 (5.2%)	169 (5.3%)
Aspartate aminotransferase (U/L) [High]	2 (0.2%)	1 (0.2%)	8 (0.3%)	7 (0.4%)	3 (0.8%)	3 (0.8%)	11 (0.3%)
Bilirubin (µmol/L) [high]	0	0	2 (0.1%)	0	0	0	2 (0.1%)
Calcium (mmol/L) [high]	0	0	2 (0.1%)	0	0	1 (0.3%)	2 (0.1%)
Calcium (mmol/L) [low]	0	0	17 (0.6%)	18 (0.9%)	0	0	17 (0.5%)
Creatinine (µmol/L) [high]	1 (0.1%)	1 (0.2%)	3 (0.1%)	6 (0.3%)	0	1 (0.3%)	3 (0.1%)
Glucose (mmol/L) [high]	27 (2.9%)	6 (1.3%)	81 (2.9%)	43 (2.3%)	29 (7.6%)	25 (6.5%)	110 (3.5%)
Glucose (mmol/L) [low]	0	0	0	0	1 (0.3%)	0	1 (0.0%)
Magnesium (mmol/L) [high]	1 (0.1%)	0	4 (0.1%)	9 (0.5%)	0	0	4 (0.1%)
Magnesium (mmol/L) [low]	1 (0.1%)	0	1 (0.0%)	1 (0.1%)	1 (0.3%)	0	2 (0.1%)
Phosphate (mmol/L) [low]	2 (0.2%)	0	40 (1.4%)	20 (1.1%)	4 (1.1%)	6 (1.6%)	44 (1.4%)
Potassium (mmol/L) [high]	1 (0.1%)	1 (0.2%)	6 (0.2%)	6 (0.3%)	3 (0.8%)	3 (0.8%)	9 (0.3%)
Potassium (mmol/L) [low]	0	4 (0.9%)	10 (0.4%)	11 (0.6%)	2 (0.5%)	3 (0.8%)	12 (0.4%)
Sodium (mmol/L) [high]	1 (0.1%)	0	1 (0.0%)	2 (0.1%)	0	0	1 (0.0%)
Sodium (mmol/L) [low]	12 (1.3%)	7 (1.5%)	40 (1.4%)	26 (1.4%)	6 (1.6%)	8 (2.1%)	46 (1.4%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

Patients were generally counted only once for each parameter. However, for parameters with both high and low criteria, patients are counted only once for each criterion (high or low), so a single patient can count towards both high and low criteria if the patient has laboratory values meeting each criterion. Summaries are based on all test results collected in the treatment-emergent period.

Grade 3 and 4 toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

Hepatic impairment

The incidence of TEAEs of hepatic impairment was lower in the enzalutamide group compared with the placebo group in both Study MDV3100-14 (1.2% vs. 1.9%) and in the phase 3 studies (1.9% vs. 2.4%).

Table 43. TEAEs of hepatic impairment

Preferred Term (MedDRA v16.1) Category n patients	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	Enzalutamide§ (n = 3179)
Any event of hepatic impairment	11 (1.2%)	9 (1.9%)	52 (1.9%)	45 (2.4%)	16 (4.2%)	17(4.4%)	68 (2.1%)
Alanine aminotransferase increased	7 (0.8%)	4 (0.9%)	20 (0.7%)	12 (0.6%)	5 (1.3%)	5 (1.3%)	25 (0.8%)
Aspartate aminotransferase increased	6 (0.6%)	3 (0.6%)	22 (0.8%)	19 (1.0%)	3 (0.8%)	7 (1.8%)	25 (0.8%)
Blood bilirubin increased	1 (0.1%)	0	3 (0.1%)	2 (0.1%)	5 (1.3%)	1 (0.3%)	8 (0.3%)
Gamma glutamyltransferase increased	1 (0.1%)	0	4 (0.1%)	0	4 (1.1%)	3 (0.8%)	8 (0.3%)
Any event of hepatic impairment leading to death	1 (0.1%)	0	2 (0.1%)	3 (0.2%)	1 (0.3%)	0	3 (0.1%)
Any serious event of hepatic impairment	2 (0.2%)	2 (0.4%)	5 (0.2%)	8 (0.4%)	5 (1.3%)	2 (0.5%)	10 (0.3%)
Any grade ≥ 3 event of hepatic impairment	5 (0.5%)	2 (0.4%)	17 (0.6%)	13 (0.7%)	4 (1.1%)	2 (0.5%)	21 (0.7%)
Any event of hepatic impairment as the primary reason for treatment discontinuation	1 (0.1%)	0	6 (0.2%)	5 (0.3%)	3 (0.8%)	2 (0.5%)	9 (0.3%)
Any event of hepatic impairment leading to dose interruption	2 (0.2%)	2 (0.4%)	5 (0.2%)	8 (0.4%)	2 (0.5%)	2 (0.5%)	7 (0.2%)
Any event of hepatic impairment leading to dose reduction	1 (0.1%)	0	2 (0.1%)	3 (0.2%)	0	0	2 (0.1%)

No hepatic impairment events met Hy's Law criteria in Study MDV3100-14, the phase 3 studies or the phase 2 studies.

Three enzalutamide-treated patients (1 in Study MDV3100-14, 1 in Study MDV3100-03 and 1 in Study MDV3100-09) died due to a TEAE of hepatic impairment. In all 3 patients, the fatal hepatic event was assessed as unrelated to the study drug by the investigator.

In general, the incidence of SAEs of hepatic impairment was low and similar among Study MDV3100-14, the phase 3 studies and the total enzalutamide group (0.2%, 0.2% and 0.3%), as was the incidence of grade ≥ 3 events of hepatic impairment (0.5%, 0.6% and 0.7%) and hepatic impairment events as the primary reason for discontinuation (0.1%, 0.2% and 0.3%).

Renal impairment

Overall, the incidence of TEAEs of renal impairment was lower in the enzalutamide group of Study MDV3100-14 compared with the placebo group (1.7% vs. 4.1%). In the phase 3 studies, the incidence of any event of renal impairment was also lower in the enzalutamide group compared with the placebo group (2.8% vs. 4.3%). The incidence of any event of renal impairment in the enzalutamide group of Study MDV3100-14 was lower than the enzalutamide group of the phase 3 studies and the total enzalutamide group (1.7% vs. 2.8% and 3.0%).

The most frequent TEAEs of renal impairment were increased blood creatinine and acute renal failure. The incidence of increased blood creatinine in the enzalutamide group of Study MDV3100-14 was lower compared with the phase studies 3 and the total enzalutamide group (0.6% vs. 1.1% and 1.2%). The incidence of increased blood creatinine was the lower in enzalutamide group compared with placebo group in both Study MDV3100-14 (1.7% vs. 4.1%) and the phase 3 studies (2.8% vs. 4.3%). Acute renal failure was the next most common preferred term. The incidence was low in the enzalutamide groups of the MDV3100-14, phase 3 studies and total enzalutamide group (0.9%, 0.8% and 0.9 %). The incidence of acute renal failure was lower in enzalutamide group compared with placebo group in both Study MDV3100-14 (0.9% vs. 1.9%) and the phase 3 studies (0.8% vs. 1.2%).

One patient in the enzalutamide group of Study MDV3100-14 and 1 patient in CRPC2 study experienced a TEAE of renal impairment leading to death.

In general, the incidence of SAEs of renal impairment was low and similar among the Study MDV3100-14, phase 3 and total enzalutamide groups (0.5%, 0.6% and 0.7%), as was the incidence of grade ≥ 3 events of renal impairment (0.5%, 1.0% and 1.1%) and renal impairment events as the primary reason for discontinuation (0.1%, 0.1% and 0.2%).

Safety in special populations

Table 44. Treatment-emergent adverse events by age group

Category, n patients (%)	MDV3100-14		Phase 3 Studies†		Phase 2 Studies‡		Total Enzalutamide§ (n = 3179)
	Enzalutamide (n = 930)	Placebo (n = 465)	Enzalutamide (n = 2799)	Placebo (n = 1898)	Enzalutamide (n = 380)	Bicalutamide (n = 387)	
Age group¶							
< 65 years	121 (13.0%)	69 (14.8%)	578 (20.7%)	425 (22.4%)	83 (21.8%)	71 (18.3%)	661 (20.8%)
65 to 74 years	367 (39.5%)	197 (42.4%)	1193 (42.6%)	808 (42.6%)	163 (42.9%)	148 (38.2%)	1356 (42.7%)
≥75 years	442 (47.5%)	199 (42.8%)	1028 (36.7%)	665 (35.0%)	134 (35.3%)	168 (43.4%)	1162 (36.6%)
Patients with any adverse event							
< 65 years	98 (81.0%)	53 (76.8%)	531 (91.9%)	377 (88.7%)	79 (95.2%)	67 (94.4%)	610 (92.3%)
65 to 74 years	315 (85.8%)	155 (78.7%)	1111 (93.1%)	723 (89.5%)	150 (92.0%)	137 (92.6%)	1261 (93.0%)
≥75 years	395 (89.4%)	152 (76.4%)	968 (94.2%)	591 (88.9%)	128 (95.5%)	151 (89.9%)	1096 (94.3%)
Patients with any grade ≥ 3 adverse event							
< 65 years	27 (22.3%)	8 (11.6%)	210 (36.3%)	139 (32.7%)	22 (26.5%)	23 (32.4%)	232 (35.1%)
65 to 74 years	105 (28.6%)	43 (21.8%)	455 (38.1%)	301 (37.3%)	56 (34.4%)	63 (42.6%)	511 (37.7%)
≥75 years	160 (36.2%)	58 (29.1%)	456 (44.4%)	255 (38.3%)	65 (48.5%)	58 (34.5%)	521 (44.8%)
Patients with any serious adverse event							
< 65 years	21 (17.4%)	6 (8.7%)	155 (26.8%)	104 (24.5%)	16 (19.3%)	12 (16.9%)	171 (25.9%)
65 to 74 years	82 (22.3%)	30 (15.2%)	350 (29.3%)	206 (25.5%)	38 (23.3%)	44 (29.7%)	388 (28.6%)
≥75 years	123 (27.8%)	49 (24.6%)	355 (34.5%)	206 (31.0%)	60 (44.8%)	43 (25.6%)	415 (35.7%)

All enrolled patients who received any amount of study drug (enzalutamide, bicalutamide or placebo) in their respective study (Safety Population).

The data cutoff date for MDV3100-14 (PROSPER) was 28 Jun 2017. The data cutoff dates for the other phase 3 studies were 15 Jan 2014, 01 Jul 2013 and 20 Sep 2015 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 19 Oct 2014 and 09 Feb 2015 for 9785-CL-0222 and MDV3100-09, respectively.

† The phase 3 studies include MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232.

‡ The phase 2 studies are 9785-CL-0222 and MDV3100-09.

§ The total enzalutamide group includes all enzalutamide-treated patients from MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222 and MDV3100-09.

¶ The n value provided in these age group rows represents the denominator used to calculate the percentages in this table of the respective age subgroups.

Discontinuation due to adverse events

Treatment-emergent adverse events leading to discontinuation

In Study MDV3100-14, the proportion of patients with TEAEs reported as the primary reason for permanent discontinuation of study drug was higher in the enzalutamide group compared with placebo (9.4% enzalutamide vs. 6.0% placebo). The phase 3 studies had similar rates of discontinuation due to TEAE in both enzalutamide and placebo groups (8.2% vs. 8.1%) as did the total enzalutamide group (8.1%).

In the MDV3100-14 enzalutamide group, the most frequent TEAEs reported as the primary reason for permanent discontinuation of study drug included fatigue (1.6%) followed by MI (0.4%), cardiac failure (0.3%), cerebrovascular accident (0.3%) and nausea (0.3%). In the phase 3 studies enzalutamide group, the most frequent TEAEs reported as the primary reason for permanent discontinuation of study drug included fatigue (0.8%) followed by nausea (0.4%) and cerebrovascular accident (0.3%).

Treatment-emergent adverse events leading to dose modification

Dose reductions

Overall, the proportion of patients with TEAEs leading to a dose reduction was higher in the enzalutamide group compared with the respective placebo group in Study MDV3100-14 (10.1% vs. 2.8%) and the phase 3 studies (4.7% vs. 1.8%).

In the MDV3100-14 enzalutamide group, the most frequent TEAEs leading to a reduction in the dose of study drug included fatigue (3.9%) followed by asthenia (1.4%) and hypertension (1.0%). In the enzalutamide group of the phase 3 studies, the most frequent TEAEs leading to a reduction in the dose of study drug included fatigue (1.6%) followed by asthenia (0.5%), nausea (0.4%), hypertension (0.3%) and dizziness (0.3%).

Dose interruptions

Overall, the proportion of patients with TEAEs leading to a dose interruption was higher in the enzalutamide group compared with the respective placebo group in Study MDV3100-14 (15.4% vs. 8.6%) and the phase 3 studies (13.2% vs. 10.8%). The incidence of TEAEs leading to a dose interruption was higher in enzalutamide group of MDV3100-14 compared with total enzalutamide group (15.4% vs. 13.4%).

For the enzalutamide groups of the MDV3100-14 and the phase 3 studies, the most frequent TEAEs leading to an interruption in the dose of the study drug were similar. In the MDV3100-14 enzalutamide group, the most frequent TEAEs leading to an interruption in the dose of study drug included fatigue (2.8%) followed by hypertension (1.3%) and decreased appetite (1.2%). The most frequent TEAEs leading to an interruption in the dose of study drug in the enzalutamide group of the phase 3 studies included fatigue (1.5%) followed by hypertension (0.8%), decreased appetite (0.7%) and asthenia (0.7%).

Post marketing experience

The cumulative exposure from marketing experience is estimated to be 184070 patient treatment-years (67922 patient treatment-years in Europe).

Six PSURs for Xtandi (enzalutamide) have been submitted to regulatory authorities since August 2012. A total of 83138 ADRs have been reported from postmarketing data sources. During the reporting period for PSUR 6, an assessment of postmarketing events revealed no safety concerns related to the 7 important identified risks (seizure, PRES, hypertension, neutrophil count decreased,

cognitive/memory impairment, fall and fracture) and 2 important identified interactions (interactions with strong inhibitors or inducers of cytochrome P450 (CYP) 2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19) listed in the current enzalutamide EU risk management plan (v 12.0, Jul 2017).

2.5.1. Discussion on clinical safety

So far, 3179 patients with prostate cancer have been treated with enzalutamide in clinical trials. The safety profile of enzalutamide for the proposed indication is based mainly on a phase 3 study (MDV3100-14 - PROSPER), in which 930 patients with nonmetastatic castration-resistant prostate cancer (CRPC) at high risk of disease progression (based on rising PSA and PSA doubling time) received enzalutamide.

The safety database includes data from the MDV3100-14 study and integrated safety data from the Phase III placebo-controlled studies i.e. MDV3100-14, MDV3100-03 (PREVAIL, conducted in asymptomatic or mildly symptomatic chemotherapy-naive patients), CRPC2 (AFFIRM, conducted in patients with metastatic CRPC who had received prior docetaxel) and 9785-CL-0232 (Asian PREVAIL) and data from two Phase II, bicalutamide-controlled studies (9785-CL-0222 [TERRAIN] and MDV3100-09 [STRIVE]).

In the study MDV3100-14 the median duration of treatment was 18.4 months in the enzalutamide group compared with 11.1 months for the placebo group, thus a higher rate of adverse events would be expectable with enzalutamide. A similar proportion of patients (33 %) received study drug in the ≥12 and < 24 months range in the respective arms however a higher proportion of enzalutamide treated patients (35%) received study drug for ≥ 24 months compared with the placebo group (13 %). The exposure was shorter for the other Phase III studies compared with study MDV3100-14 likely due to these patients experiencing more advanced disease.

The population included in the study MDV3100-14 was well balanced between treatment groups. It encompasses patients with a median age of 74 years (47.5% of patients were 75 years or older), with nonmetastatic disease (97%) and a good performance status (baseline ECOG 0 in 80% of patients and ECOG 1 in 19.9% of patients). Approximately 21% of enzalutamide-treated patients had medical history of hypertension. Patients with past history of seizure or conditions that predispose to an increased risk of seizure, creatinine values > 2 mg/dL, unacceptable haematology values, liver chemistry tests more than twice the upper limit of normal (ULN) or any clinically significant cardiovascular disease were excluded.

Overall, the incidence of TEAEs was higher in the enzalutamide group compared with the placebo group (86.9% vs. 77.4%, respectively) with the most commonly reported TEAEs (≥ 5% of patients) being fatigue (32.6% vs. 13.8%), hot flush (13.0% vs. 7.7%), hypertension (11.9% vs. 5.2%), nausea (11.4% vs. 8.6%), fall (11.4% vs. 4.1%), dizziness (9.8% vs. 4.3%), decreased appetite (9.6% vs. 3.9%), constipation (9.1% vs. 6.9%), headache (9.1% vs. 4.5%), asthenia (8.8% vs. 6.0%) and weight decreased (5.9% vs. 1.5%). When adjusted for the duration of treatment, differences versus placebo were reduced; fatigue, decreased appetite and hypertension remained higher in the enzalutamide group (≥ 2% higher incidence compared to placebo). In general, a lower incidence of TEAEs was reported in the pivotal study as compared to the integrated data sets.

TEAEs considered by the investigator to be drug-related were reported in 62.4% of patients treated with enzalutamide and 45.4% of patients in the placebo group. Of these, fatigue, decreased appetite,

hypertension, weight decreased, dizziness and dysgeusia were at least twice more frequently reported in the enzalutamide arm.

Grade 3 or higher AEs were reported in 31.4% of patients treated with enzalutamide compared to 23.4% in the placebo arm. Hypertension (4.6% enzalutamide vs. 2.2% placebo), fatigue (2.9% vs. 0.6%), syncope (1.1% vs. 0.4%), fall (1.3% vs. 0.6%), asthenia (1.2% vs. 0.2%) and pneumonia (1.1% vs. 0.4%) were grade≥ 3 AEs more frequent (≥ 0.5% higher incidence) in the enzalutamide group than in the placebo group.

AEs considered of special interest reported during study MDV3100-14 include seizure, cognitive and memory impairment, neutrophil count decreased, hypertension, fatigue, select cardiovascular events, hepatic impairment, second primary malignancies, falls, fractures, syncope and renal impairment. These were selected based on previously recognised important identified risks and/or feedback from regulatory authorities recommending surveillance.

In the enzalutamide group 3 patients (0.3%) experienced a seizure, which were considered by the investigator as possibly related to study drug. No patient in the placebo group reported any event of seizure. In the combined enzalutamide group, 13 (0.4%) events were reported (relevant warning reflected in SmPC).

The incidence of TEAEs of any event of neutrophil count decreased was higher in enzalutamide treated patients compared to placebo (MDV3100-14: 0.9% vs. 0.2%; Phase III studies: 1.4% vs 0.6%). In the total enzalutamide group the proportion was 1.4 %, none fatal. The incidences were low for serious TEAEs (0.1 %), grade ≥ 3 events (0.7 %) and as the primary reason for permanent discontinuation (0.1 %). Dose interruptions and dose reductions due to neutrophil count decreased were 0.2 % and 0.1 % in the total enzalutamide dataset, respectively. There were no reports of cases of febrile neutropenia. Of the nine patients reported with TEAEs of neutropenia, two cases were identified with concurrent infections. One case with cough Grade 1 (Day 286) which did not result in either hospitalisation or discontinuation from study (discontinuation subsequently occurred on Day 409 due to PD) and a second patient that had what seems like a transient event of neutropenia grade 1 during which time he experienced and was treated for a herpes zoster infection (no action was taken in terms of study drug).

Major adverse cardiovascular events (MACE) were reported in a higher number of patients in the enzalutamide group compared with the placebo group (5.2% vs. 2.8%, respectively) and so did grade 3 or higher MACE. When adjusted for treatment duration, those differences remained higher in the enzalutamide arm (4.1 vs. 2.9) although in line with data from previous phase 3 studies. In patients with baseline history of cardiovascular disease event rates were slightly higher (9.9 enzalutamide and 8.6 placebo vs. 2.6 enzalutamide and 1.5 placebo).

Hypertension is a common adverse event of enzalutamide, reflected in the SmPC. In study MDV3100-14 hypertension was reported in 12.3% of patients treated with enzalutamide compared with 5.4% of patients that received placebo. No differences were observed in the incidence of hypertension according to baseline history of hypertension (12.1% history of hypertension vs. 11.7% no history of hypertension).

Fatigue and asthenia are common adverse events related to enzalutamide treatment. In study MDV300-14 fatigue was reported in 32.6% of patients treated with enzalutamide compared with 13.8% with placebo. Additionally, fatigue is a common symptom in patients with advanced cancer, so a lower incidence would be expected in patients with nonmetastatic disease. In contrast, the incidence of fatigue in study MDV300-14, in patients with no metastatic disease and a better performance status, was similar to that reported in previous phase III trials in patients with metastatic disease.

Adverse events of fractures were reported in 11.2% of patients treated with enzalutamide compared to 5.5% with placebo. The incidence increases with the longer exposure to study treatment. Similar proportions were observed in the combined Phase III safety dataset (10.2% vs. 4.4%) as well as in the enzalutamide group (10.3%). A similar difference between enzalutamide and placebo remained when adjusted for treatment duration all through the presented safety datasets. This is reflected in the SmPC.

Most commonly types of fracture reported in enzalutamide treated patients in the MDV3100-14 were rib fracture (4.2%), spinal compression fracture (1.8%), femur fracture (0.5%) and upper limb fracture (0.5%). The study protocol did not include a required assessment of fractures as "non-pathological" vs. "pathological", therefore the proportion of pathological vs. non-pathological fractures in enzalutamide vs. placebo treated patients cannot be reliably elucidated.

The incidence of fall was higher in the enzalutamide treated patients compared to placebo (106 [11.4%] vs. 19 [4.1%]). This was also observed when adjusting for treatment duration (9.5% vs. 4.1%). A post-hoc analysis revealed that 51/106 patients in the enzalutamide group and 10/19 in the placebo arm experienced a fracture within two days of a reported fall. Thus, 49% of patients that reported a fracture in the enzalutamide arm and 38.5% in the placebo arm had suffer from a previous fall.

A higher incidence of second primary malignancies, excluding nonmelanoma skin cancers, was reported in the enzalutamide group compared to the placebo group (2.9% vs. 1.1%, respectively). When adjusted for treatment duration, event rates per 100 patient-year remained higher in the enzalutamide group (2.1 enzalutamide vs. 1.0 placebo). Similar data have been reported in patients treated with enzalutamide in the Phase III studies (2.4% vs. 0.9%) and in the total enzalutamide group (2.5%). Second primary malignancies were reported across a variety of different organ systems and cell types. A total of five patients in the integrated safety population were identified with second primary malignancies considered by the investigator to be possibly or probably drug-related. However, no obvious mechanistic rationale for androgen receptor inhibition to cause specifically these malignancies can be established. Enzalutamide has shown to be carcinogenic in non clinical trials. The relevance of these findings in humans is unknown, but the potential risk of enzalutamide to develop second primary malignancies cannot be ruled out (see 5.3 of SmPC). Furthermore, due to the non-clinical findings related to urinary bladder carcinogenicity of enzalutamide, a signal will be triggered to further study these pre-clinical findings and relevance for human use.

For both renal and hepatic impairment the incidences were lower in the enzalutamide arm as compared to placebo in the pivotal study (renal impairment 1.7% vs. 4.1%; hepatic impairment 1.2% vs. 1.9%). No Hy's Law cases were identified. One fatality due to renal impairment occurred in the MDV3100-14 study not deemed related to study drug. It is to be noted that patients with advanced renal or hepatic impairment were not eligible into the MDV3100-1334 study.

The incidence of SAEs in the enzalutamide group was higher than in the placebo group (24.3% vs. 18.3%), although only in 3.4% of patients that received enzalutamide SAEs were considered related to study drug by the investigator. In addition, differences between treatment arms were driven mainly by the higher number of SAEs reported in the enzalutamide group after one year of treatment compared to placebo (106 [11.4%] enzalutamide vs. 24 [5.2%] placebo). In the enzalutamide group, hematuria and pneumonia were the only SAEs reported in ≥ 1%. SAEs reported in a higher percentage of patients in the enzalutamide group (incidence ≥0.5% or double) were pneumonia, atrial fibrillation, fall, cardiac failure myocardial infarction and coronary artery disease.

As of the data cutoff, 103 (11.0%) and 62 (13.2%) patients had died in the enzalutamide and placebo y group, respectively. The majority of deaths were due to disease progression (5.4% enzalutamide vs.

9.7% placebo). A higher number of deaths were related to AEs in the enzalutamide group compared to placebo group (32 [3.4%] enzalutamide vs. 3 [0.6%] placebo), with myocardial infarction as the main AE resulting in death in the enzalutamide arm. Additionally, there were 3 deaths of unknown cause in the enzalutamide group and a higher number of deaths occurred within 30 days after discontinuation of study drug.

Regarding safety in special populations, no important safety issues have been identified. According to baseline weight (≤ median vs. > median) the incidence of AEs, SAEs and ≥ 3 AEs appear similar between groups (data not shown). AEs were analysed per age group, < 65 years (13.0%), 65 to 74 years (39.5%) and ≥ 75 years (47.5%). The frequency of AEs of any grade, AEs of grade ≥ 3, and SAEs increased with each age group but it is expectable due do the increased sensitivity for AEs with increasing age.

Patients with baseline history of hypertension, reported a higher incidence of AEs of any grade (88.9% history of hypertension vs. 83.7% no history of hypertension), SAEs (27.1% vs. 20.1%) and AEs of grade ≥ 3 (34.6% vs. 26.6%) compared to patients without baseline history of hypertension and compared to patients that received placebo. Within SAEs and Grade ≥ 3 AEs, a higher incidence of cardiac disorders was reported in patients with a baseline history of hypertension compared to those without previous history of hypertension (SAEs: 5.3% vs. 2.4%; Grade ≥3 TEAEs: 5.9% vs. 2.2%). These differences were lower in the placebo group and in the combined phase 3 population. However, considering the combined phase 3 studies and after adjusting for treatment duration, a similar trend of a higher incidence of cardiac disorders in patients with previous history of hypertension was observed in both treatment arms (enzalutamide and placebo).

Additionally, the applicant has provided an analysis of other risk factors and the presence of selected cardiovascular events (defined as Myocardial Infarction and Other Ischemic Heart Disease) and overall a similar pattern was observed. It should be noted that the incidence of cardiovascular AEs was higher in those patients with a previous history of cardiac failure treated with enzalutamide. However, this higher incidence would be expected. Moreover, ischemic heart disease has been included in section 4.8 of the SmPC as a common AE, and included as an important identified risk in the RMP.

The incidence of AEs of any grade was higher in patients from North America compared to patients from Europe and patients from the rest of the world (91.5% vs. 85.3% vs. 87.1%, respectively) whereas the frequency of SAEs was lower in that subgroup of patients and no great differences were observed in the incidence of grade 3 or higher AEs.

Treatment discontinuations as well as dose reductions or dose interruptions were relatively low in the enzalutamide group (9.4%; 10.1% and 15.4%, respectively), although higher than in the placebo group (6.0%; 2.8% and 8.6%). The most common AEs leading to treatment discontinuation were fatigue (1.6%), MI (0.4%), cardiac failure, cerebrovascular accident and nausea (0.3%, each). Overall, enzalutamide seems to be well tolerated.

The safety profile of enzalutamide in the study MDV3100-14 is in line with the known safety profile of enzalutamide. Compared with previous clinical trials, in which most of the patients had metastatic disease, a lower incidence of AEs of any grade, grade ≥ 3 AEs and SAEs were reported in the enzalutamide group in study MDV3100-14. However, regarding study drug-related AEs and grade ≥ 3 AEs incidence, no differences were observed.

2.5.2. Conclusions on clinical safety

Overall, enzalutamide seems to be well tolerated. The safety profile of enzalutamide in patients with nonmetastatic castration resistant prostate cancer appears similar to that reported in previous clinical trials, with no major safety concerns. Relevant information is reflected in the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.5 is acceptable.

The CHMP endorsed the Risk Management Plan version 12.5 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Seizure • Fall • Non-pathological fracture • Ischemic heart disease
Important potential risks	• None
Missing information	• None

"Ischemic heart disease" was identified as a new safety concern as part of this extension of indication. Data from the studies supportive of the new indication showed a higher incidence of ischemic heart disease events between enzalutamide and placebo-treated patients. Due to the clinical significance of ischemic heart disease events and causal relationship ischemic heart disease was added as an important identified risk.

Some of the existing important identified risks and missing information were removed from the list of safety concerns as a result of the transition to the new RMP template revision 2 in accordance with the new GVP module V.

Pharmacovigilance plan

No additional pharmacovigilance activities were requested as a result of the new indication.

Routine pharmacovigilance activities remain sufficient to mitigate the safety concerns of Xtandi.

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Seizure	Routine risk communication: • SmPC sections 4.4, 4.7, 4.8, and 4.9; • PL sections 2 and 4; • Recommendation that the decision to continue treatment in patients who develop seizure should be taken case by case, is provided in SmPC section 4.4 and PL sections 2 and 4; • Concomitant medications associated with higher risk of seizure are described in PL section 2. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Fall	Routine risk communication: • SmPC section 4.8; • PL section 4. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fall and Fracture TDQ in clinical trials; • Safety analyses of events of fall in CSRs of individual enzalutamide clinical trials. Additional pharmacovigilance activities: • None.
Non-pathological fracture	Routine risk communication: • SmPC section 4.8; • PL section 4. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fall and Fracture TDQ in clinical trials; • Safety analyses of events of fracture in CSRs of individual enzalutamide clinical trials. Additional pharmacovigilance activities: • None.
Ischemic heart disease	Routine risk communication: • SmPC section 4.8; • PL section 4. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Safety analyses of events of ischemic heart disease in CSRs of individual enzalutamide clinical trials. Additional pharmacovigilance activities: • None.

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities

CSR: Clinical Study Report; PL: package leaflet; SmPC: Summary of Product Characteristics; TDQ: targeted data questionnaire.

No additional risk minimisations measures were requested as a result of the new indication.

Routine risk minimisation measures remains sufficient to mitigate the safety concerns of Xtandi.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 5.1 and 5.3 of the SmPC have been updated.

In addition, following the review of the clinical studies results, sections 4.4, 4.5, 4.7, 4.8, 5.2 and 6.6 of the SmPC were updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s).

Please refer to attachment 1 for the full detail of the Product Information updates.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xtandi 40 mg and 80 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication is for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (PSADT ≤10 months).

3.1.2. Available therapies and unmet medical need

Current treatment options are limited. Although continued use of ADT is part of clinical practice, no therapy is approved specifically for the treatment of patients with nonmetastatic CRPC or for prevention of metastasis, and patients are encouraged to participate in clinical studies.

3.1.3. Main clinical studies

Efficacy data in support of this application focus on data from trial MDV3100-14 (PROSPER): A multinational, phase 3, randomized, double-blind trial in which Enzalutamide (160 mg once daily)

administered add-on to ADT was compared to ADT plus placebo in a total of 1401 men (2:1) with non-metastatic castration-resistant prostate cancer (CRPC) who had rapidly rising PSA (PSA doubling time ≤ 10 months). 1401 patients were randomised in at 2:1 proportion. All patients had a short PSADT (stratified for <6 months or > 6 months but <10 months).

3.2. Favourable effects

Results from PROSPER trial in the efficacy target population of patients at the cut-off date of 28-June-2016 included the main analysis planned for MFS (BIRC assessed) and the first interim analysis for OS (2 IA planned plus 1 final analysis).

With an event rate of 23.5% and 48.7% for enzalutamide and placebo arms respectively, a statistically significant improvement in MFS was observed for enzalutamide compared to placebo (HR: 0.292; 95% CI: 0.241, 0.352). The median MFS (95% CI) was 36.6 months (95% CI: 33.1, NR) in the enzalutamide group and 14.7 months (95% CI: 14.2, 15.0) in the placebo group (Δ 21.9 months). A reduction in both bone metastases and soft tissue metastases was observed among patients treated with enzalutamide compared to placebo. These results are supported by several sensitivity analyses as well as by subgroups analyses.

Overall, key secondary endpoints showed consistency with primary efficacy outcomes. Treatment with enzalutamide delayed time to PSA progression (HR:0.066; 95% CI: 0.054, 0.081) and time to first use of new antineoplastic treatment (HR:0.208; 95% CI: 0.168, 0.258). OS data, still immature at the time of the second IA (31 May 2018) so as to draw any firm conclusion (event rate 19.7% and 22.2% in enzalutamide and placebo arms respectively), did not cross the boundary for statistical significance (HR= 0.832, 95% CI: 0.654, 1.059) and no clear separation of the survival curves is observed.

Other secondary efficacy endpoints included to provide additional evidence of clinical benefit (need for First Use of Cytotoxic Chemotherapy, Chemotherapy-Free Disease-Specific Survival, Chemotherapy-Free Survival) though still immature in some cases, all supported primary efficacy results but time to pain progression (HR:0.959; 95% CI: 0.801, 0.1.149).

3.3. Uncertainties and limitations about favourable effects

There is uncertainty related to the long-term effects of enzalutamide on Overall Survival and relevant secondary endpoints. A post-authorisation efficacy study (PAES) in order to investigate the long-term effects of enzalutamide on Overall Survival and relevant secondary endpoints in adult men with high-risk non-metastatic castration-resistant prostate cancer. The MAH should submit the results of the MDV3100-14 (PROSPER) efficacy study.

3.4. Unfavourable effects

Overall, enzalutamide was well tolerated, since the number of discontinuations as well as dose modifications were relatively low. The safety profile of enzalutamide was in line with the already known safety profile, with no major differences compared to previous clinical trials in terms of the incidence and severity of AEs.

The overall incidence of AEs in the enzalutamide group was 86.9% (compared to 77.4 in the placebo group), 62.4% of whom were considered by the investigator to be related to study drug. The most commonly reported AEs were fatigue (32.6%), hot flush (13.0%), hypertension (11.9%), nausea (11.4%), fall (11.4%), dizziness (9.8%), decreased appetite (9.6%), constipation (9.1%), headache (9.1%), asthenia (8.8%) and weight decreased (5.9%). Exposure to treatment was longer with

enzalutamide compared to placebo. When adjusted for the duration of treatment, fatigue, decreased appetite and hypertension were higher in the enzalutamide group.

Grade ≥ 3 were reported in 31.4% of patients treated with enzalutamide. Hypertension (4.6% enzalutamide vs. 2.2% placebo), fatigue (2.9% vs. 0.6%), syncope (1.1% vs. 0.4%), fall (1.3% vs. 0.6%), asthenia (1.2% vs. 0.2%) and pneumonia (1.1% vs. 0.4%) were grade≥ 3 AEs more frequent (≥ 0.5% higher incidence) in the enzalutamide group than in the placebo group.

AEs considered of special interest reported during study MDV3100-14 include seizure, cognitive and memory impairment, neutrophil count decreased, hypertension, fatigue, cardiovascular events, hepatic impairment, second primary malignancies, falls, fractures, syncope and renal impairment.

SAEs were reported in 24.3% of patients in the enzalutamide group, although only in 3.4% of patients that received enzalutamide SAEs were considered related to study drug by the investigator. Haematuria and pneumonia were the only SAEs reported in ≥ 1%.

Treatment discontinuations as well as dose reductions or dose interruptions were relatively low in the enzalutamide group (9.4% vs. 10.1% vs. 15.4%, respectively). The most common AEs leading to treatment discontinuation were fatigue (1.6%), MI (0.4%), cardiac failure, cerebrovascular accident and nausea (0.3%, each).

3.5. Uncertainties and limitations about unfavourable effects

A higher event rate of second primary malignancies has been reported in patients treated with enzalutamide compared to placebo (2.1 enzalutamide vs. 1.0 placebo), which is in line with data from previous clinical trials with enzalutamide. Enzalutamide has shown to be carcinogenic in non-clinical trials (related to urinary bladder carcinogenicity). The relevance of these findings in humans is unknown, but the potential risk of enzalutamide to develop second primary malignancies cannot be ruled out, also considering the longer exposure expected in the new proposed indication in patients with non metastatic castration-resistant cancer. Relevant information has been included in section 5.3 of the SmPC. A signal will be triggered to further study these pre-clinical findings and relevance for human use.

3.6. Effects Table

Table 45. Effects Table

Effect	Short description	Unit	Enzalutamide (plus ADT)	Placebo (plus ADT)	Uncertainties / Strength of evidence
Favourable Effects					
MFS	Metastasis Free Survival	Median mo (95%CI)	36.6 (33.1, NR)	14.7 (14.2, 15.0)	Main analysis with 23.5% of events in Enzal arm vs. 48.7% events in Pl arm. HR (95% CI): 0.292 (0.241, 0.352)
Time to PSA progression		Median mo (95%CI)	37.2 (33.1, NR)	3.9 (3.8, 4.0)	22.3% of events in Enzal arm vs. 69.2% events in Pl arm.
Time to first use of new antineoplastic therapy	Key-Secondary	mo (95%CI)	39.6 (37.7, NR)	17.7 (16.2, 19.7)	15.2% of events in Enzal arm vs. 69.2% events in Pl arm.
OS	Overall	mo	NR	NR	1st IA with 11% of events in

Effect	Short description	Unit	Enzalutamide (plus ADT)	Placebo (plus ADT)	Uncertainties / Strength of evidence
	Survival	(95%CI)	(NR, NR)	(NR, NR)	Enzal arm vs. 13.2% in Pl arm HR (95% CI): 0.795 (0.580, 1.089)
Time to pain progression	Secondary	mo (95%CI)	18.5 (17.0,22.1)	18.4 (14.8, 22.1)	42.8% of events in Enzal arm vs. 37.4% events in Pl arm.
Time to first use of cytotoxic chemotherapy	Secondary	mo (95%CI)	NR (38.1, NR)	39.7 (38.9, 41.3)	9.1% of events in Enzal arm vs. 20.5% events in Pl arm.
Unfavourable Effects					
Grade ≥ 3 TEAEs	Treatment Emergent AEs of grade 3 or higher	%	31.4%	23.4%	
Serious AEs	Adverse events considered serious	%	24.3%	18.3%	
AEs discontinuation	Adverse events as primary reason for study drug discontinuation	%	9.4%	6.0%	
Ischemic heart disease			5.2%	2.8%	
Second primary malignancies			2.9%	1.1%	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results in terms of OS failed to show any statistically significant result and data are still rather immature so as to firmly conclude about a survival benefit. However, the positive trend observed in this latter variable seems to rule out a detrimental effect. The rest of the variables provide additional evidence of clinical benefit (need for First Use of Cytotoxic Chemotherapy, Chemotherapy-Free Disease-Specific Survival, Chemotherapy-Free Survival) even though the immaturity of some of these data preclude to draw firm conclusions. All in all, there is no doubt that from a patient perspective, the fact of delaying the onset of metastases represents a value in itself, which may postpone the expected symptomatology associated to the metastatic setting. The latter is also deemed valuable in the frame of a non-curable disease where the increase in the time to progression should be weighed against the toxicity of the treatment. However, the optimal use of enzalutamide in the course of castration-resistant prostate cancer remains unknown.

Despite that a clear statistically significant reduction in terms of MFS was demonstrated in the pivotal trial, there was no unequivocal impact on overall quality of life, as indicated by patient reported outcomes. Therefore, clinical benefit in this regard must be assumed from the nature of the primary endpoint (delaying the onset of symptoms and likely deterioration of quality of life as well as the need for more aggressive treatments in the metastatic setting), in the absence of more mature OS data or alternatively in terms of relief of disease symptomatology (time to pain progression) or delaying the time to chemotherapy.

Overall, in the absence of detrimental toxicity or marked decrease in quality of life due to treatment before development of metastases, delaying metastatic disease by a considerable amount is a valid objective of therapy and that this endpoint is indicative of clinical benefit per se.

The safety profile of enzalutamide in the treatment of non-metastatic CRPC patients who had rapidly rising PSA, was in line with the already known safety profile, with no major differences compared to previous clinical trials in terms of the incidence and severity of AEs. Overall, enzalutamide was well tolerated.

3.7.2. Balance of benefits and risks

To date, no therapy is currently approved for progression from nonmetastatic to metastatic CRPC. The current clinical guidelines include watchful waiting as one of the strategies in this setting, reflecting the absence of any treatments having been proven valuable.

Results from PROSPER trial are considered to demonstrate a clinically and statistically significant advantage in terms of MFS for patients with high-risk non-metastatic CRPC, without indications of a detrimental effect on overall survival, whereas the safety profile of enzalutamide was acceptable. The benefit-risk balance was concluded to be positive. The finally approved indication was restricted to more accurately reflect the high-risk M0 CRPC population.

3.7.3. Additional considerations on the benefit-risk balance

There is uncertainty related to how the introduction of enzalutamide prior to development of metastasis could influence in later lines (cross-resistance). Although PFS2 data could shed some light in this issue, this was not included as endpoint in the pivotal trial. It remains unknown whether the best use of enzalutamide is in the present line of therapy or rather in later lines, where an OS benefit has been shown. However, determining the optimal sequencing of available agents throughout the course of the disease is a complex task that falls outside the scope of this marketing authorisation. Such studies are encouraged.

3.8. Conclusions

The Benefit/risk for enzalutamide in the treatment of high-risk non-metastatic castration resistant prostate cancer is positive.

The CHMP considers the following measures necessary to address issues related to efficacy:

A post-authorisation efficacy study (PAES) in order to investigate the long-term effects of enzalutamide on Overall Survival and relevant secondary endpoints in adult men with high-risk non-metastatic castration-resistant prostate cancer. The MAH should submit the results of the MDV3100-14 (PROSPER) efficacy study.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

C.I.4: Update of sections 4.4, 4.5, 4.7, 4.8, 5.2 and 6.6 of the SmPC in order to amend the warning on possible association with seizure, to amend the effects on driving or operating machines, to amend the identified adverse reactions and to amend the 'Race' subsection regarding pharmacokinetic properties based on the results from the completed studies PROSPER, a Phase 3 Randomized Controlled Study, designed to investigate the Safety and Efficacy of Enzalutamide in Patients with Non-Metastatic Castration-Resistant Prostate Cancer; and Asian PREVAIL, a Multinational Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Oral Enzalutamide in Chemotherapy-naive Subjects with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy; and the updated integrated clinical safety database.
The Package Leaflet is updated in accordance. In addition, the Product Information was updated according to the latest QRD template.

C.I.6.a: Extension of Indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC) for Xtandi, as a consequence, sections 4.1, 5.1 and 5.3 of the SmPC are updated, based on the supportive clinical study results of MDV3100-14 (PROSPER), a Phase 3 Randomized Controlled Study, designed to investigate the Safety and Efficacy of Enzalutamide in Patients with Non-Metastatic Castration-Resistant Prostate Cancer; MDV3100-09 (STRIVE), a Multicenter Phase 2 Study to investigate the Safety and Efficacy of Enzalutamide Versus Bicalutamide in Men With Non-Mtastatic or Metastatic Castration-Resistant Prostate Cancer; and based on supportive non-clinical data from 7 new reports.
The Package Leaflet is updated in accordance.

An update RMP version 12.5 was agreed.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in

accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to investigate the long-term effects of enzalutamide on Overall Survival and relevant secondary endpoints in adult men with high-risk non-metastatic castration-resistant prostate cancer, the MAH should submit the results of the MDV3100-14 (PROSPER) efficacy study:	
The Interim Analysis report of OS should be submitted by:	January 2020
The final clinical study report should be submitted by:	December 2023

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) The Package Leaflet is updated in accordance.

Update of SmPC to amend the warning on possible association with seizure, to amend the effects on driving or operating machines, to amend the identified adverse reactions and to amend the ‘Race’ subsection regarding pharmacokinetic properties based on the results from the completed studies

PROSPER (Phase 3 Randomized Controlled Study) and Asian PREVAIL (Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study) and the updated integrated clinical safety database. The Package Leaflet is updated in accordance. In addition, the Product Information was updated according to the latest QRD template.

Summary

Please refer to the scientific discussion Xtandi EMEA/H/C/002639/II/0039G.

Attachment

1. SmPC, Annex II, Labelling and Package Leaflet (changes highlighted) as adopted by the CHMP on 20 September.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 10 October 2018. The principles to be applied for the deletion of CCI are published on the EMA website at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.