EUROPEAN UNION LOCAL RISK MANAGEMENT PLAN

ENZALUTAMIDE (XTANDI®)

The Astellas Group

Astellas Pharma Inc.
2-5-1, Nihonbashi-Honcho, Chuo-ku,
Tokyo 103-8411, Japan

Astellas Pharma Global Development, Inc.
One Astellas Way,
Northbrook, IL 60062, United States

Astellas Pharma B.V.
Sylviusweg 62,
2333 BE Leiden, The Netherlands

EU Local Risk Management Plan for XTANDI (Enzalutamide)

RMP version to be assessed as part of this application:

RMP Version number: 18.0

Data lock point for this RMP: 31 Jan 2023*

* The data lock point for postmarketing data (exposure, adverse event data) and epidemiology data is 31 Jan 2023. For clinical trial data: the data lock point for 9785-CL-0335 (ARCHES) is 28 May 2021 and for MDV3100-14 (PROSPER) is 15 Oct 2019; the data lock points for the other phase 3 studies are 21 Mar 2019, 20 Feb 2018 and 04 Nov 2020 for MDV3100-03, CRPC2, and 9785-CL-0232, respectively; the data lock points for the phase 2 studies are 17 Feb 2018 and 30 May 2018 for 9785-CL-0222 and MDV3100-09, respectively. The data lock point for MDV3100-13 (EMBARK) is 31 Jan 2023.

Date of final sign-off: Refer to date of final signature on the electronic signature page

Rationale for submitting an updated RMP:	The RMP version 17.0 was updated to include the results from the phase 3 study, MDV3100-13 (EMBARK). The new indication proposed in the updated RMP version 18.0 is treatment of adult men with high-risk biochemical recurrence (BCR) nonmetastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy. Removal of ARCHES for other forms of routine pharmacovigilance activities. TDQs for Fall and Fracture to apply only to spontaneous cases. The safety concerns have not changed and were reviewed in accordance with Good Pharmacovigilance Practices (GVP) Module V Rev. 2 (Mar 2017).
Summary of significant changes in this RMP:	Additional data from the phase 3 study MDV3100-13 (EMBARK) was added in the RMP to Part I, Table I.1 and multiple modules under Part II. The safety concerns have not changed in this version. Part II, SI and Annex 7: Epidemiology information has been updated. Part II, SV: Postauthorization exposure has been updated. Description of ARCHES has been removed from Other Forms of Routine Pharmacovigilance Activities under Part III, III.1. ARCHES CSR was completed and submitted to EMA procedure (EMEA/H/C/002639/II/0057) where EU RMP version 17.0 was approved. TDQs for Fall and Fracture to apply only to spontaneous cases.

Other RMP versions under evaluation:

Not Applicable

Details of the currently approved RMP:

Version number:	17.0
Approved with procedure:	EMEA/H/C/002639/II/0057
Date of approval (opinion date)	10 Mar 2022

QPPV approval/oversight:

European Qualified Person Responsible for Pharmacovigilance

Astellas Pharma Europe B.V.

The Netherlands

QPPV signature: Electronic signature appended at the end of the document

List of Abbreviations

Abbreviation	Definition
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
ASIR	Age Standardized Incidence Rate
ASMR	Age Standardized Mortality Rate
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Classification
AUC	Area Under The Plasma Concentration-Time Curve
BA	Bioavailability
BCR	Biochemical Recurrence
BCRP	Breast Cancer Resistance Protein
BE	Bioequivalence
BMD	Bone Mineral Density
BRCA	Breast Cancer
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum Drug Concentration
CN	Chemotherapy Naïve
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR_{CL}	Creatinine Clearance
CRF	Case Report Form
CRPC	Castration-Resistant Prostate Cancer
CSPC	Castration-Sensitive Prostate Cancer
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DB	Double Blind
DBP	Diastolic Blood Pressure
DDI	Drug-drug Interaction
DLP	Data Lock Point
dMMR	Deficient Mismatch Repair
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
EAU	European Association of Urology

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
ENZA	Enzalutamide
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life-5 Dimensions- 5 Levels
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GABA	Gamma Aminobutyric Acid
GnRH	Gonadotropin-releasing Hormone
GPRD	General Practice Research Database
GVP	Good Pharmacovigilance Practices
HDL	High-density Lipoprotein
HIV	Human Immunodeficiency Virus 1
HPCG1	Hereditary Prostate Cancer Gene
HR	Hazard Ratio
HSPC	Hormone-Sensitive Prostate Cancer
IARC	International Agency for Research on Cancer
IC	Inhibitory Concentration
IHD	Ischemic Heart disease
INN	International Nonproprietary Name
ISS	Integrated Summary of Safety
LDL	Low-Density Lipoprotein
LHRH	Luteinizing Hormone-Releasing Hormone
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis Free Survival
MI	Myocardial Infarction
mPCa	Metastatic Prostate Cancer
MRP	Multidrug Resistant-Associated Protein
MSI-H	Microsatellite Instability-high
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application

nmCRPC	Nonmetastatic Castration-Resistant Prostate Cancer
NNH	Number Needed to Harm
NOAEL	No Observable Adverse Effect Level
NPCR	National Prostate Cancer Register
NYHA	New York Heart Association
OAT	Organic Anion transporter
OCT	Organic Cation Transporter
OL	Open Label
OS	Overall Survival
PBO	Placebo
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary Embolism
PFS	Progression Free Survival
P-gp	P-glycoprotein
PL	Package Leaflet
PRES	Posterior Reversible Encephalopathy Syndrome
PSA	Prostate-Specific Antigen
PSADT	Prostate-specific Antigen Doubling Time
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Person-years or Patient-years
RANKL	Receptor Activator of Nuclear Factor-Kb-Ligand
RMP	Risk Management Plan
rPFS	Radiographic Progression Free Survival
RR	Relative Risk
SBP	Systolic Blood Pressure
SCS	Summary of Clinical Safety
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results (Programme)
SERM	Selective Estrogen Receptor Modulators
SIR	Standardized Incidence Ratio
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SMR	Standardized Mortality Ratio
SOC	System Organ Class
TDQ	Targeted Data Questionnaire
TEAE	Treatment-emergent Adverse Event
UK	United Kingdom

ULN	Upper Limit of Normal
US	United States
USPSTF	United States Preventive Services Task Force

Table of Contents

PART I: PRODUCT OVERVIEW

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

Table Part I.1: Product Overview

Active substance {International Nonproprietary Name [INN] or common name}	Enzalutamide
Pharmacotherapeutic group(s) Anatomical Therapeutic Classification (ATC) Code	L02BB04
Marketing Authorization Holder	Astellas Pharma Europe B.V.
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	XTANDI®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Enzalutamide is a potent androgen receptor signaling inhibitor that blocks several steps in the androgen receptor-signaling pathway.
	Summary of mode of action Enzalutamide competitively inhibits binding of androgens to androgen receptors, inhibits nuclear translocation of activated receptors and inhibits the association of the activated AR with DNA even in the setting of androgen receptor 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 tumor regression. In nonclinical studies, enzalutamide lacks androgen receptor agonist activity.
	Important information about its composition Not applicable
Hyperlink to the product information	[Module 1.3.1; SmPC]

Indication(s) in the EEA	Current (if applicable): XTANDI is indicated for: ● The treatment of adult men with high risk nonmetastatic castration-resistant prostate cancer (CRPC); ● The treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated; ● The treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy. ● The treatment of adult men with metastatic hormone-sensitive prostate cancer (HSPC).
	Proposed (if applicable): ● Treatment of adult men with high-risk biochemical recurrence (BCR) nonmetastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy.
Dosage in the EEA	Current (if applicable): ● 160 mg (four 40 mg oral capsules once daily); ● 160 mg (four 40 mg oral film-coated tablets once daily or two 80 mg oral film-coated tablets once daily).
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Enzalutamide is formulated in the surfactant caprylocaproyl macrogolglycerides (LABRASOL®). The product is provided as 40 mg liquid-filled soft gelatin capsules for oral administration. Enzalutamide is also provided as 40 mg film-coated tablets and 80 mg film-coated tablets, both for oral administration.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

AR: Androgen Receptor; ATC: Anatomical Therapeutic Chemical; BCR: Biochemical Recurrence; CRPC: Castration-Resistant Prostate Cancer; DNA: Deoxyribonucleic Acid; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; nmHSPC: Nonmetastatic Hormone-Sensitive Prostate Cancer; RMP: Risk management Plan; SmPC: Summary of Product Characteristics

PART II: SAFETY SPECIFICATION

PART II: MODULE SI. EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

XTANDI® (enzalutamide [MDV3100]) is indicated for the treatment of adult men with nonmetastatic castration-resistant prostate cancer (nmCRPC) and for the treatment of adult men with metastatic CRPC (mCRPC) whose disease has progressed on or after docetaxel therapy, as well as for the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated. XTANDI® is also indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC). It is proposed that indication be expanded for the treatment of adult men with high-risk biochemical recurrence (BCR) nonmetastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage- radiotherapy. Hormone-sensitive prostate cancer can be defined as prostate cancer that responds to androgen deprivation suppression therapy. Patients diagnosed with nmHSPC are commonly asymptomatic at this stage and do not present clinical evidence of metastases [de Sa Moreira et al, 2021]. This section presents information on the epidemiology of the overall prostate cancer population, and where possible, the epidemiology of the CRPC prostate cancer populations (mCRPC and nmCRPC) and HSPC (mHSPC and nmHSPC).

Incidence:

Incidence of prostate cancer in Europe

In 2020, the annual, age-standardized incidence of prostate cancer in Europe was estimated to be 63.4 per 100 000 males (using the world standard population), with an estimated 473 344 newly diagnosed cases of prostate cancer in Europe in 2020 [Sung et al, 2021]. The incidence of prostate cancer in the European Union (EU) was higher in older age groups, ranging from 0.05 per 100 000 males among those aged 15 to 39 years to 629 per 100 000 males among those aged 70 years or older [Sung et al, 2021]. In the recent years, incidence rates have plateaued or declined in some European countries [Bray et al, 2018] with the highest rates in Ireland, Estonia, and Sweden [Ferlay et al, 2020]. Refer to Annex 7, Table 1 and Table 2, for additional estimates of prostate cancer incidence in Europe.

Incidence of prostate cancer in the rest of the world

Prostate cancer is the second most frequent diagnosed malignancy (after lung cancer) in men worldwide, accounting for more than 1.4 million new cases and 375 304 deaths (3.8% of all deaths caused by cancer in men) in 2020 [Wang, 2022]. The crude incidence rate was estimated at 36.0 per 100 000 males in 2020 and the age standardized incidence rate (ASIR) was estimated at 30.7 per 100 000 males. ASIRs in Europe, Latin America and the Caribbean, Northern America and Oceania exceeded 59 per 100 000 males, while ASIRs in Africa and Asia were lower than 30 per 100 000 males. However, the regional distribution of age standardized mortality rates (ASMRs) was quite different, with the highest rate in Africa,

followed by Latin America and the Caribbean, Europe, Oceania, Northern America and Asia [Wang, 2022].

Prostate cancer is the most frequently diagnosed cancer among men in over one half of the countries of the world, including countries in the Americas, Northern and Western Europe, and much of Sub-Saharan Africa, and in Australia and New Zealand [Bray et al, 2018]. Globally, the incidence rate of prostate cancer varies across regions and populations [Rawla, 2019]. The worldwide variations in prostate cancer incidence may in part be attributed to the prostate-specific antigen (PSA) testing [Quinn et al, 2002].

Prostate cancer incidence increases with age [Rawla, 2019]. Although only 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer [Perdana et al, 2016], the incidence rate increases to 1 in every 52 men for ages 50 to 59 years and is considerably higher in men over the age of 65 years [Rawla, 2019].

Incidence of newly diagnosed metastatic prostate cancer (mPCa)

There is limited published literature on the stage-specific incidence of prostate cancer in Europe. The International Agency for Research on Cancer (IARC) databases do not provide stage-specific prostate cancer incidence data. An epidemiologic study conducted in 25 public hospitals in Spain, reported that 3.8% of all newly diagnosed prostate cancer cases (n = 4025) in the year 2010 presented as metastatic disease [Cozar et al, 2013]. Stage-specific prostate cancer incidence data collected by the United States (US) Surveillance Epidemiology and End Results (SEER) registries indicated that 5% of all newly diagnosed prostate cancer cases during the years 2008 to 2014 presented as distant metastatic disease [Noone et al, 2018]. Some studies have reported an increase in the annual rate of newly diagnosed metastatic prostate cancer using the SEER database. Bandini et al, reported that the age-adjusted incidence of newly diagnosed mPCa increased from 1.9 to 2.4 cases per 100 000 population between 2004 and 2014 [Bandini et al, 2018]. In another study, Kelly et al, using SEER database, investigated the change in incidence of mPCa over years and predicted incidence trends and the number of new cases expected each year. In their study, mPCa steadily declined from 2004 to 2007 by 1.45%/yr and began to increase by 0.58%/yr after 2008, which accelerated to 2.74%/yr following the 2012 United States Preventive Services Task Force (USPSTF) recommendations [Kelly et al, 2018].

Incidence of mHSPC

As described in the above sub-section, the incidence of newly diagnosed metastatic prostate cancer comprises approximately 4% to 5% of all newly diagnosed prostate cancer cases, based on the hospital-based study published by Cózar and colleagues (2013) and the US SEER registries' data [Noone et al, 2018]. Data describing estimates of prostate cancer patients with localized disease who experience disease recurrence with metastases, and who also are mHSPC cases, are scarce. However, de Velasco Oria de Rueda et al, in a Spanish multicenter, observational study in routine clinical practice of patients diagnosed with mHSPC between 2015 and 2019 reported incidence ranging from 2.2-3.0% [de Velasco Oria de Rueda et al, 2022].

Data describing the incidence of metastases in patients with localized prostate cancer may provide context for the number of localized prostate cancer patients who progress as mHSPC cases. According to a study in the United Kingdom (UK), the estimated incidence of metastases in patients with localized prostate cancer following surgery or radiotherapy was 2.4 and 3.0 per 1000 person-years (PY), respectively, and 6.3 per 1000 PY in patients undergoing active surveillance [Hamdy et al, 2016].

Incidence of nmHSPC

No population based studies on the incidence of nmHSPC in the EU or the US were identified. Additionally, no population-based studies are available on the proportion of patients diagnosed with nmHSPC with high-risk BCR in the EU or the US.

Incidence of CRPC

There are limited population-based data describing the incidence of CRPC. A retrospective population-based study conducted in the UK using the General Practice Research Database (GPRD) identified castrated patients who developed CRPC from 1999 through 2009 (which represented 28% of all castrated prostate cancer patients during this period) [Hirst et al, 2012]. The estimated incidence of CRPC was 8.3 per 100 patient years (PY) among castrated prostate cancer patients and 3.8 per 100 PY among all prostate cancer patients. In a population-based cohort study of prostate cancer patients identified in Northern and Central Denmark Regions, during 1997 to 2010, 80% of 2494 nonmetastatic prostate cancer patients, who were treated with ADT, developed CRPC during follow-up (mean follow-up = 20 months) [Nguyen-Nielsen et al, 2015].

Incidence of mCRPC

There is limited information on the incidence of mCRPC in the epidemiologic literature. Hirst and colleagues (2012) evaluated the incidence of mCRPC UK GPRD and reported an incidence rate of mCRPC of 6.4 per 100 PYs [Hirst et al, 2012]. Most males with CRPC die of prostate cancer and most deaths due to prostate cancer occur in males with CRPC [Kelly et al, 2012; Smith et al, 2012; Scher et al, 2011]. Some males who develop mCRPC were first diagnosed with metastatic prostate cancer while others were initially diagnosed with earlier-stage prostate cancer that eventually progressed to mCRPC. One approach to estimating the incidence of CRPC among the general male population in Europe would be to assume that (1) prostate cancer inevitably progresses to castration-resistance in males with advanced disease who are treated with ADT and (2) these patients do not die from other causes. The age-standardized mortality rate due to prostate cancer in Europe, standardized to the world standard population, was estimated at 11.1 per 100 000 males, and may be considered as an estimate of the incidence of mCRPC in the EU [Annex 7, Table 5].

Incidence of nmCRPC

No population-based studies on the incidence of nmCRPC in the EU or the US were identified.

Prevalence:

Prevalence of prostate cancer in Europe

European country-specific 1-, 3- and 5-year partial prevalence estimates for prostate cancer are provided by IARC [Sung et al, 2021]. The 5-year partial prevalence of prostate cancer in the EU was reported as 518.1 per 100 000 males [Sung et al, 2021]. The 5-year partial prevalence estimated for the individual member countries of the EU ranged from 319.8 per 100 000 males in Romania to 905.5 per 100 000 males in Sweden [Sung et al, 2021]. The 1-, 3-, and 5- year partial prevalence for each of the member states of the EU can be found in Annex 7, Table 3.

Prevalence of metastatic prostate cancer

No population-based data describing the prevalence of metastatic prostate cancer in Europe are available. An alternative approach to estimating the prevalence of metastatic prostate cancer in Europe employs stage IV data from the US SEER registries. Stage IV prostate cancer includes disease with distant metastases, locally advanced disease, and disease with regional lymph node involvement that is not amenable to local treatment with curative intent, and thus is generally broader than the mPCa population. The prevalence of stage IV prostate cancer in the EU was estimated based on data from the US SEER database and data on all prostate cancer from IARC [Ferlay et al, 2018a; SEER Program, 2018]. Assuming that the 15-year prevalence of stage IV prostate cancer in the EU was similar to that among White males in the US at the same time (i.e., 0.03%), the number of males with stage IV prostate cancer in the EU may be estimated as the male population in the EU on 01 Jan 2015 (approximately 248 million) [Eurostat Database; 2018] multiplied by 0.03%, resulting in an estimated 74470 males alive in the EU with stage IV prostate cancer. This estimate may be biased by regional differences in PSA screening practices, rate of progression of localized disease to locally advanced or metastatic disease after diagnosis, under-representation of non-Whites, and the misclassification of stage IV disease as “unknown” stage in the SEER database. Additional partial prevalence data for stage IV prostate cancer can be found in Annex 7, Table 4.

Prevalence of mHSPC

As described under the sub-section, *Prevalence of metastatic disease*, estimates of prevalent metastatic prostate cancer cases are not available. Alternatively, an estimate of the prevalence of stage IV prostate cancer in the EU is based on the 15-year prevalence of stage IV prostate cancer in the US and data on all prostate cancer from IARC [SEER Program, 2018]. It is estimated that 74 470 males were alive in the EU with stage IV prostate cancer on 01 Jan 2015.

Prevalence of nmHSPC

A study conducted in Spain suggests that the period prevalence of nmHSPC is much more common than other subtypes at diagnosis in the general population (nmHSPC 68.2%; mHSPC 14.6%; nmCRPC 5.0%; mCRPC 12.1%) [de Velasco Oria de Rueda et al, 2022]. No

other population-based studies on the prevalence of nmHSPC in the EU, or the US were available.

Prevalence of CRPC

There are no prevalence data available on CRPC for any European country. Data from a systematic literature review indicated that 10% to 20% of prostate cancer patients in the UK and US develop CRPC within 5 years of follow-up [Kirby et al, 2011; Alemayehu et al, 2010; Bianco Jr et al, 2003]. However, the studies cited by these authors varied in selection of the population used for the denominator of this calculation. Thus, these proportions should not be applied directly to prevalence of CRPC among the general population of all males with prostate cancer.

Prevalence of mCRPC

There are no population-based studies on the prevalence of mCRPC. However, a large database study in the UK reported an estimate of metastatic disease of 15.7% among CRPC patients [Hirst et al, 2012]. Using a prostate cancer clinical states progression model, Scher and colleagues (2015) estimated a prevalence of mCRPC of 72 690 in the US in 2017 [Scher et al, 2015].

Prevalence of nmCRPC

There are no peer-reviewed publications describing the prevalence of nmCRPC using population-based data. Using available data from 1990 to 2009, Scher et al (2015) utilized a dynamic progression model to predict the impact of current treatment algorithms for nmCRPC on the future prevalence of nmCRPC, along with the mortality of the men diagnosed with prostate cancer for the period 2009 through 2020 in the US. Based on projected improvement in progression free survival (PFS) in early nmCRPC, the model predicted that improved PFS will result in an increase in the prevalence of nmCRPC by 12% (139 22 more patients) relative to the 2020 baseline prevalence of 112 410 patients [Scher et al, 2015].

Demographics of the Population - Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease:

Prostate cancer occurs exclusively in males. Several well-established risk factors for prostate cancer include age, race/ethnicity and family history [Brawley, 2012; Patel et al, 2009]. The majority of prostate cancer cases are diagnosed among older age groups; in the EU in 2020, 95% of males diagnosed with prostate cancer were aged 55 years or older, and 50% were aged 70 years or older [Sung et al, 2021]. In the US, the incidence rate of prostate cancer in black males (184.2 per 100 000) exceeded the incidence rates in white (111.5 per 100 000), Asian/Pacific Islander (59.3 per 100 000), American Indian/Alaska native (73.2 per 100 000), and Hispanic males (86.9 per 100 000) during the years (2016-2020) [SEER, 2022]. The percent of distant metastatic disease among newly diagnosed prostate cancer cases has also varied by race. Of all prostate cancer cases recorded in the US SEER registry (2004-2012), distant metastatic disease was present in 4.2% of non-Hispanic whites, 5.8% of Hispanic whites, 5.7% of blacks, 5.5% of Asian/Pacific Islanders, and 8.8% of American

Indian/Alaska natives [Bernard et al, 2017]. Additional demographic data can be found in Annex 7, Table 2.

Several pieces of evidence point to a genetic factor associated with the development of prostate cancer. First, the likelihood of developing prostate cancer more than doubles for a male whose father or a brother has been affected by this disease. Additionally, mutations in hereditary prostate cancer gene 1 (HPCG1) and breast cancer (BRCA) 1 and 2 tumor suppressor genes have been correlated with an onset of prostate cancer. Genetic studies suggest that strong familial predisposition may be responsible for 5% to 10% of prostate cancers [Brawley, 2012]. The precise relationship between environmental and exogenous factors (such as diet) and prostate cancer onset remains unclear [Brawley, 2012].

Main existing treatment options:

Treatment of mHSPC

Initially, the growth of prostate cancer is stimulated by androgens and may be inhibited by ADT in the form of surgical or medical castration. For newly diagnosed metastatic prostate cancer patients, guidelines published by the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) suggest offering surgical castration in the form of orchiectomy, or medical castration in the form of a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist [NCCN, 2019; Mottet et al, 2018; Cornford et al, 2017]. Additionally, combining castration with chemotherapy (docetaxel), or with abiraterone acetate plus prednisone, is recommended for metastatic prostate cancer patients who are fit [Mottet et al, 2018]. Castration with or without an antiandrogen is recommended for metastatic prostate cancer patients who are unfit for treatment with docetaxel or abiraterone plus prednisone [Mottet et al, 2018]. In particular, an antiandrogen can be offered to metastatic patients treated with LHRH agonists in order to reduce testosterone flare.

Treatment of nmHSPC

Treatment options are limited among patients with high-risk nmHSPC with evidence of recurrence by PSA but without overt metastases. For these patients, standard of care options includes systemic treatment with ADT; orchiectomy or luteinising hormone-releasing hormone agonist [LHRHa] or LHRH antagonist), salvage local therapy, usually with radiotherapy (RT) or observation. There is no general clinical consensus on optimal ADT timing either with early treatment to delay progression and prolong survival or with later treatment once metastases and symptoms develop to lessen the risk of adverse effects [Freedland et al, 2021].

Treatment of mCRPC

Over time, patients with mCRPC generally experience continued disease progression, worsening pain, and become eligible for chemotherapy. Although first line chemotherapy with docetaxel plus prednisone demonstrated a survival benefit in these patients [Tannock et al, 2004], its use leads to substantial morbidity from severe neutropenia, diarrhea, and other toxicities. Other treatment options that have demonstrated a survival improvement in patients

with mCRPC after docetaxel include cabazitaxel plus prednisone [de Bono et al, 2010], abiraterone plus prednisone [de Bono et al, 2011], and enzalutamide [Scher et al, 2012]. Studies with enzalutamide have also shown survival improvement and reduced risk of radiographic progression in chemotherapy-naïve patients with mCRPC [Beer et al, 2017; Merseburger et al, 2015; Beer et al, 2014].

All patients with mCRPC should maintain castrate levels of serum testosterone. The NCCN recommends the following therapies for mCRPC without visceral metastases: sipuleucel-T, abiraterone with prednisone, docetaxel with prednisone, enzalutamide, and radium-223 (the latter for symptomatic bone metastases), as well as secondary hormone therapy (antiandrogen, antiandrogen withdrawal, ketoconazole, corticosteroids, or diethylstilbestrol). Treatment options for mCRPC with visceral metastases include the above therapies (with docetaxel and prednisone as the preferred first-line chemotherapy), as well as alternative chemotherapy (mitoxantrone with prednisone) for palliative benefit for patients who cannot tolerate docetaxel. Radium-223 is not recommended in these patients. Participation in clinical trials is encouraged in both settings [NCCN, 2019]. Patients with mCRPC with progression after enzalutamide or abiraterone have the following treatment options: docetaxel, abiraterone with prednisone (if previously given enzalutamide), enzalutamide (if previously given abiraterone), radium-223 for bone-predominant disease without visceral metastases, sipuleucel-T if asymptomatic or minimally symptomatic and without visceral metastases (life expectancy >6 months, and Eastern Cooperative Oncology Group (ECOG) score 0-1), pembrolizumab if microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR), clinical trial, or secondary hormone therapy [NCCN, 2019]. Patients with mCRPC with progression after docetaxel have the following treatment options: abiraterone/prednisone and enzalutamide (provided these agents were not used previously), radium-223 for bone-predominant disease without visceral metastases, cabazitaxel, sipuleucel-T if asymptomatic or minimally symptomatic and without visceral metastases (life expectancy > 6 months, and ECOG score 0-1), pembrolizumab if MSI-H/dMMR, clinical trial, docetaxel rechallenge, mitoxantrone with prednisone, or secondary hormone therapy [NCCN, 2019].

Treatment of nmCRPC

There is no standard of care for the management of nmCRPC due to the heterogeneity of the disease entity, with some men exhibiting indolent, slow growing process, while others experience a more rapid progression and development of metastases. No therapy was approved specifically for the treatment of patients with nmCRPC prior to 2018.

Although high-risk nmCRPC (i.e., for patients with a short PSA doubling time) is a serious disease state, current treatment options are limited. The European Society for Medical Oncology guidelines advised ADT and watchful waiting [Parker et al, 2015]. 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 nmCRPC 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].

The US NCCN guidelines recommend continued observation for patients with nmCRPC with a prostate-specific antigen doubling time (PSADT) ≥ 10 months, as they are likely to have indolent disease with a lower risk of progression to mCRPC. However, for patients with PSADT < 10 months, treatment is recommended with a goal of delaying time to development of metastases. If patients are on an antiandrogen agent at the time of progression, antiandrogen withdrawal is recommended as the first therapeutic intervention [NCCN, 2019; Sartor et al, 2008; Small et al, 2004; Dupont et al, 1993]. For treatment of nmCRPC, the NCCN guideline recommends first-generation antiandrogens (e.g., bicalutamide, nilutamide, flutamide), second-generation novel hormonal therapies (apalutamide, enzalutamide, abiraterone), ketoconazole, corticosteroids or diethylstilbestrol as second-line hormonal therapies [NCCN, 2019]. Beyond that, enrollment in a clinical trial is recommended, given the lack of compelling data identifying a clear standard of care in this population, although additional hormonal manipulations are commonly employed. In 2018, the US Food and Drug Administration (FDA) approved enzalutamide for use in nmCRPC patients. In the same year, the standard of care published by the American Urological Association for nmCRPC patients at high risk of developing metastases was apalutamide or enzalutamide with continued androgen deprivation [Cookson et al, 2018]. In 2019, FDA approved darolutamide for nmCRPC based on ARAMIS, a multicenter, double-blind, placebo-controlled clinical trial [Fizazi et al, 2019].

Natural history of the indicated condition in the population, including mortality and morbidity:

Prostate cancer is the third most common cause of cancer death among males in Europe. [Sung et al, 2021]. IARC provides the most current, estimated mortality rates from all prostate cancer in the EU [Table 5]. The mortality rate ranged from 5.9 per 100 000 males in Italy to 21.8 per 100 000 males in Estonia.

The mortality rate due to prostate cancer increases markedly with age. Annual mortality rates for the EU in 2020 ranged from 0.03 per 100 000 males among those aged 0 to 44 years to 197.7 per 100 000 males among those aged 70 years or older, with an estimated 81.8% of prostate cancer deaths occurring among males aged 70 years or older [Sung et al, 2021]. Within Europe, prostate cancer mortality rates decreased in Northern and Western Europe during the years, 2002 to 2012 [Bray et al, 2018; Wong et al, 2016]. In contrast, mortality rates in several Central and Eastern European countries rose during that time period. Worldwide, prostate cancer is the fifth leading cause of death from cancer in men, comprising 6.8% of all cancer deaths in men [Sung et al, 2021]. In 2020, 375 304 deaths due to prostate cancer were estimated to have occurred worldwide, and the annual, age-standardized mortality rate of prostate cancer worldwide was 7.7 per 100 000 males [Sung et al, 2021]. ASIRs vary more than 123-fold among 174 countries, wherein the highest ASIR was 110.7 per 100 000 males in Ireland from Northern Europe while the lowest ASIR was 0.9 per 100 000 males in Bhutan from South-Central Asia. Similarly, ASMRs varied by more than 77-fold among 174 countries, from the lowest ASMR of 0.54 per 100 000 males in Bhutan from South-Central Asia to the highest ASMR of 41.7 per 100 000 males in Zimbabwe from Eastern Africa, for which the crude mortality rate was only 12.2 per 100 000

[Wang et al, 2022]. Refer to Annex 7, Table 5 and Table 6, for additional estimates of prostate cancer mortality. There were no regional or national mortality rates for metastatic disease, or for CRPC patients reported for Europe or the US.

The EUROCARE-5 dataset provides survival data of oncology patients in 29 European countries [Trama et al, 2015]. In the EUROCARE-5 dataset, data from 87 cancer registries were accessed in order to present observed and relative survival data for patients diagnosed with prostate cancer between 2000 and 2007 and followed through 2008. Refer to Annex 7, Table 7 for the age-specific and age-standardized, observed and relative survival estimates in Europe for prostate cancer. Five-year observed and relative survival for all prostate cancer cases was 69.7% and 83.4%, respectively.

The US SEER registries provide stage-specific survival data for prostate cancer. A median overall survival (OS) of 25 months for prostate cancer patients with de novo metastatic disease was reported for cases diagnosed during the years 2004 to 2012 [Bernard et al, 2017]. The 5-year relative survival for distant metastatic prostate cancer in the US was 30% during the years 2008 to 2014 [Noone et al, 2018]. Refer to Annex 7, Table 8, for US SEER relative survival data of prostate cancer patients, stratified by age, race, and stage. There were no regional or national survival data for CRPC patients reported for Europe or the US.

Important co-morbidities:

The management of prostate cancer is often complicated by other age-related pre-existing diseases or comorbidities. The prevalence of comorbidities in patients with prostate cancer has been reported in various European studies using validated, database-derived comorbidity indices. The most frequently reported comorbidities from these studies included cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, peripheral vascular disease, hypertension, hyperlipidemia, and diabetes [Hupe et al, 2018; Ye et al, 2017; Ording et al, 2016; Nguyen-Nielsen et al 2013; Xiao et al, 2013; Li et al, 2012]. See additional details regarding reported comorbidities in Annex 7, Table 9.

Adverse effects specifically associated with ADT or with docetaxel may be relevant given that CRPC patients may have been treated with these therapies in the past, and these adverse effects could still be present in a patient when enzalutamide is started. ADT is associated with osteoporosis and fractures, adverse metabolic effects, and increased cardiovascular morbidity and mortality [Poulsen et al, 2019; Wallander et al, 2019; Hupe et al, 2018; Ng HS et al, 2018; Østergren et al, 2018; Lassemillante et al, 2014]. The major metabolic effects of ADT include decreased muscle mass and increased fat mass (together known as sarcopenic obesity), alterations in lipids, and decreased insulin sensitivity [Mitsuzuka & Arai, 2018; Smith et al, 2006; Smith, 2004; Singh et al, 2002; Smith et al, 2001]. Studies also suggest that LHRH agonists and Orchiectomy for prostate cancer are associated with clinically significant impairment in cognitive functioning [Tae et al, 2018; Crawford et al, 2017; Jim et al, 2010]. Docetaxel is associated with neutropenia, febrile neutropenia, thromboembolic events, and endocrine disorder [Purshouse and Protheroe, 2019; James et al, 2016; Sweeney et al, 2015]. Additional information describing adverse effects associated with ADT and docetaxel in prostate cancer patients can be found in Annex 7.

PART II: MODULE SII. NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Data-lock point for this Module	15 Oct 2019
Version when Module last updated	15.0

A panel of *in vitro* and *in vivo* safety pharmacology studies, *in vitro* genetic toxicity testing, embryo-fetal toxicity studies, oral repeat-dose toxicity and toxicokinetic studies and *in vitro* and *in vivo* metabolism studies, as well as 26-week and 104-week carcinogenicity studies have been conducted in mice and rats, respectively. This panel of studies is considered to have adequately assessed the nonclinical safety profile of the enzalutamide drug product.

Two safety-related effects identified from nonclinical studies were considered relevant for human use of enzalutamide in the CRPC population: Pro-convulsive potential and Effect on reproduction/fertility.

Key safety findings from nonclinical studies

Key safety findings (from nonclinical studies)	**Relevance to human usage**
Toxicity findings include:	
Moribundity Unscheduled deaths and moribund conditions occurred in both enzalutamide- and vehicle treated animals.	Moribund condition was partly due to aspiration of enzalutamide in rats and dogs and due to agonal respiration after convulsions in mice, none of which are observed in humans treated with enzalutamide.
Pro-convulsive Potential	
In pharmacology studies, enzalutamide and its active metabolite M2 bound to the GABA-gated chloride channel ($GABA_A$ receptor) in a rat brain extract. A functional assessment in α1β3- $GABA_A$ expressing Xenopus oocytes showed that enzalutamide and M2 act as $GABA_A$ antagonists. Enzalutamide and M2 were shown to cross the blood-brain barrier in mice and rats. Foster and colleagues determined that $GABA_A$ inhibition was an off-target effect for enzalutamide, noting that enzalutamide caused dose-dependent convulsions in mice after 2 days of dosing at 200 mg/kg [Foster et al, 2011]. Convulsions were observed in the repeated dose toxicity studies of enzalutamide and M2. Convulsions were observed in 1 rat (100 mg/kg per day enzalutamide in 2-week study) and 2 dogs (60 mg/kg per day enzalutamide in 4-week study; 45 mg/kg/day enzalutamide in 39-week study) and there was a dose dependent increase of convulsions	Published data support an association between $GABA_A$ antagonists and convulsions. Plasma exposures for doses of enzalutamide and M2 that were associated with convulsions in mice (200 mg/kg/day and 100 mg/kg/day, respectively) were at least 3.3-fold and 2-fold higher, respectively, than patients receiving 160 mg/day enzalutamide. Events of seizure were observed in patients with mCRPC treated with enzalutamide 160 mg/day and a pattern of dose relationship was observed in Study S-3100-1-01; however, the observed seizure cases with available pharmacokinetic data in Study CRPC2 did not provide sufficient data to confirm whether higher exposure to enzalutamide is associated with seizure. Seizure is considered an important identified risk for enzalutamide. The risk of seizure may be increased in patients who exceed the recommended daily dose of 160 mg.

in mice (200 mg/kg per day for 7 days). Convulsions were also observed in mice dosed with M2 (≥ 100 mg/kg/day in 4- week study).	
Effects on Reproduction and Fertility	
Changes in organ weights of male reproductive organs, such as the prostate, seminal vesicles, epididymis and testes and atrophic changes in the prostate, seminal vesicles, testes and epididymis were observed in studies in mice up to 4-weeks, rats up to 26-weeks, and dogs up to 39-weeks duration. Increase in embryo-fetal deaths and skeletal/external abnormalities (cleft palate, decreased anogenital distance) were observed in mice. Such effects are likely attributed to AR inhibition, as similar effects in rodents have been found for other AR antagonists [Iswaran et al, 1997; Takano et al, 1966]. In rabbits, no effects on dams or on embryo-fetal development were found up to the highest dose tested, with NOAEL for both of 10 mg/kg per day. Studies in pregnant rats showed that enzalutamide and/or its metabolites are transferred to fetuses. Enzalutamide and/or its metabolites are secreted in rat milk.	Effects on fertility have not been assessed, but enzalutamide would be expected to impair male fertility, at least transiently. Based on current knowledge of the effects of enzalutamide and other anti-androgens on embryo-fetal development, the use of enzalutamide is contraindicated in females who are or may become pregnant. Use of enzalutamide may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant. It is not known if enzalutamide is present in human milk.
Mutagenicity, Genotoxicity	
Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay, was non-mutagenic, non-clastogenic in mammalian cells, and non-genotoxic in vivo in mice.	There is no evidence of mutagenicity, clastogenicity or genotoxicity in humans given enzalutamide.
Carcinogenicity	
In a 26-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day, which resulted in plasma exposure levels similar to the clinical exposure in metastatic CRPC patients receiving 160 mg, daily. In a 2-year study in Wistar Han rats, enzalutamide at doses up to 100 mg/kg/day, induced benign thyoma in the thymus, benign Leydig cell tumor in the testes, granulosa cell tumor in the ovaries, adenoma in the pas distilis in the pituitary, and fibroadenoma in the mammary glands (males only). Urothelium papilloma and carcinoma of the urinary bladder were observed but considered likely to be due to continuous irritation caused by small kidney stones (urinary crystals/calculi) which is more pronounced in rats because of anatomical differences and positioning	There is no evidence of carcinogenicity in humans given enzalutamide. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out. Tumors in the testes, mammary glands and ovaries have also been reported in rats treated with other antiandrogens such as bicalutamide [Iswaran et al, 1997] or flutamide [Eulexin, 2001], although the potential relevance to humans is unknown. Humans with advanced cancer are not likely to be impacted by the occurrence of enzalutamide-related tumors. Urinary bladder tumors, secondary to crystal/calculi are not expected to occur in humans due to upright positioning of the bladder. Additionally, the incidence of

of the urinary bladder (horizontal in rat versus upright in human).	bladder calculi reported in the clinical trials with enzalutamide was found to be comparable between the enzalutamide and placebo groups.
General safety pharmacology findings:	
Effects on Endocrine Organs	
Several histopathological findings in endocrine tissues were observed in rats, which included hypertrophy/hyperplasia in the adrenal gland, pituitary, and thyroid, atrophy in the male mammary gland, gland/lumen dilatation and lobular hyperplasia in the female mammary gland, and luminal dilatation in the uterus. Leydig cell hypertrophy and/or hyperplasia were observed in the 4-week study for enzalutamide metabolite M2 in mice and the 39- week study for enzalutamide in dogs. All these findings, except for the mammary gland changes in both genders and the pituitary changes in females, were found to be reversible.	No AEs of pituitary hypertrophy or hyperplasia have been reported in clinical studies for enzalutamide. While adrenal and pituitary hypertrophy were observed in nonclinical studies for bicalutamide, flutamide and nilutamide, no signals for altered adrenal or pituitary function have been observed clinically [Baltogiannis et al, 2004; Reid et al, 1999; De Leo et al, 1998]. These findings indicate that the adrenal and pituitary effects that were observed in the 26-week rat toxicity study are unlikely to translate to humans. Effect on the mammary gland may occur in patients treated with ADT. Leydig cell hypertrophy/hyperplasia is not relevant for CRPC patients, as these have undergone orchiectomy or use LHRH analogs. The extensive clinical experience with anti-androgens has shown that Leydig cell tumors in animals do not translate to a risk for humans [Cook et al, 1999].
Effects on the Gastrointestinal Tract	
Emesis, fecal changes (loose, soft, and/or discolored feces) and salivation occurred in dogs.	Gastrointestinal AEs such as nausea, vomiting, and diarrhea are commonly observed with other anti-androgen treatments. Although the overall incidence of events within the Gastrointestinal disorders SOC was higher among enzalutamide-treated patients in the phase 3 studies, when adjusted for length of exposure, the event rates for these common gastrointestinal events and overall events within the Gastrointestinal disorders SOC were markedly lower in the enzalutamide group compared with the placebo group in the phase 3 controlled population [Module 5.3.5.3 ISS/SCS, Tables 14.3.1.2.1.1 and 14.3.1.2.6].
Drug Interactions	
In vitro data indicate that enzalutamide may be an inhibitor of the transporters P-gp, BCRP, MRP2, OAT3 and OCT1. Enzalutamide may increase the oral	Oral medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., colchicine, dabigatran etexilate, digoxin), BCRP, MRP2, OAT3 or OCT1

bioavailability or total body clearance of P-gp, BCRP, MRP2, OAT3 and OCT1 substrates.	(e.g., methotrexate) should be used with caution when administered concomitantly with enzalutamide and may require dose adjustments to maintain optimal plasma concentrations.

ADT: Androgen Deprivation Therapy; AE: Adverse Event; AR: Androgen Receptor; BCRP: Breast Cancer Resistant Protein; CRPC: Castration-Resistant Prostate Cancer; FDA: Food and Drug Administration; GABA: Gamma Aminobutyric Acid; ISS: Integrated Summary of Safety; LHRH: Luteinizing Hormone-Releasing Hormone; MRP2: Multidrug Resistant-Associated Protein 2; NDA: New Drug Application; NOAEL: No-Observed Adverse Effect Level; OAT: Organic Anion Transporter; OCT: Organic Cation Transporter; P-gp: P-glycoprotein; SCS: Summary of Clinical Safety; SOC: System Organ Class.

PART II: MODULE SIII. CLINICAL TRIAL EXPOSURE

Data-lock point for this Module	The data cutoff date for MDV3100-14 (PROSPER) was 15 Oct 2019 and 9785-CL-0335 (ARCHES) was 28 May 2021. The data cutoff dates for the other phase 3 studies were 21 Mar 2019, 20 Feb 2018 and 04 Nov 2020 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data cutoff dates for the phase 2 studies were 17 Feb 2018 and 30 May 2018 for 9785-CL-0222 and MDV3100-09 respectively. The data lock point for MDV3100-13 (EMBARK) was 31 Jan 2023.
Version when Module last updated	18.0

CRPC: Castration-resistant Prostate Cancer

SIII.1 Clinical Trial Exposure Relevant for Tablet Formulation

The 5 biopharmaceutic studies assessing the tablet used the approved capsule as reference for formulation comparisons and evaluated the pharmacokinetics either after a single 160 mg dose or after multiple-dose administration at 160 mg/day. Four of these studies assessed the relative bioavailability of various development tablets (Tablets A, B, C, E, and F) and 1 study (9785-CL-0014) was a pivotal bioequivalence study of the to-be-marketed tablet.

See [Table SIII.1] for a summary of the 5 biopharmaceutic studies evaluating tablet formulations.

Table SIII.1 Summary of Biopharmaceutic Studies Evaluating Tablet Formulations

	Single-dose Studies (160 mg)				Multiple-dose Study (160 mg/day)
Design feature	**Study MDV3100-05**	**Study 9785-CL-0010**	**Study MDV3100-19**	**Study 9785-CL-0014**	**Study 9785-CL-0003**
Tablet formulation	Tablet A	Tablets B and C	Tablets E and F	To-be- marketed tablet	Tablet A
Table strength	160 mg	80 mg	80 mg	80 mg	160 mg
Pharmacokinetic objectives	Relative BA and food effects	Relative BA	Relative BA	Pivotal BE and food effects	Relative BA and food effects
Subjects	Healthy males	Healthy males	Healthy males	Healthy males	CRPC patients
Number of subjects treated	60	55	45	59	27
Food conditions	Fasted and fed	Fasted	Fasted	Fasted and fed	Fasted and fed
Design for formulation comparison	2-period crossover	1-period parallel group	1-period parallel group	2-period crossover	1-period parallel group
Design for food-effect comparison	Parallel group	NA	NA	Parallel group	Crossover

Tablets A, B, C, E, and F were development tablet formulations.

All studies used soft gelatin capsules containing enzalutamide (4 x 40 mg) as the reference treatment. For studies with 80 mg tablets, 2 x 80 mg tablets were administered to achieve the 160 mg dose.

BA: Bioavailability; BE: Bioequivalence: CRPC: Castration-Resistant Prostate Cancer; NA: Not Applicable

Source: Enzalutamide (MDV3100) Tablets (80 and 40 mg) CTD Module 2.5 Clinical Overview, Table 2.

Demographic characteristics of the study population are presented by study in [Table SIII.2]. Baseline characteristics were generally consistent across treatment groups in the healthy

subject studies. The healthy subjects were all males and were predominantly White, although there was a higher proportion of Black or African American males in both MDV3100-05 and MDV3100-19 than in the other studies. In 9785-CL-0003, the male subjects with CRPC were significantly older than subjects in the healthy subject studies, as would be expected for a CRPC population.

Table SIII.2 Summary of Demographics for Studies MDV3100-05, 9785-CL-0010, MDV3100-19, 9785-CL-0014, and 9785-CL-003 (Safety Analysis Sets)

Baseline Characteristics	Study MDV3100-05			Study 9785-CL-0010			Study MDV3100-19			Study 9785-CL-0014			Study 9785-CL-0003		
	Fasted (n=30)	Fed (n=30)	Total (n=60)	Capsule (n=19)	Tablet B (n=19)	Tablet C (n=18)	Capsule (n=14)	Tablet E (n=16)	Tablet F (n=15)	Fasted (n=29)	Fed (n=30)	Total (n=59)	Capsule (n=13)	Tablet (n=14)	Total (n=27)
Age															
Mean (Standard Deviation)	28.1 (7.37)	30.5 (10.27)	29.3 (8.95)	33.8 (10.96)	41.1 (8.98)	43.2 (7.77)	34.9 (8.37)	32.9 (11.33)	34.1 (9.92)	43.3 (9.0)	41.0 (10.6)	42.1 (9.8)	70.2 (8.1)	70.0 (9.5)	70.1 (8.7)
Median	27.5	27.0	27.0	32.0	43.5	44.5	34.5	30.5	32.0	47.0	44.5	45.0	70.0	69.0	70.0
Min, Max	19, 42	19, 55	19, 55	20, 51	26, 55	29, 54	20, 49	19, 52	19, 50	27, 55	20, 55	20, 55	59, 88	57, 92	57, 92
Race†															
White	25 (83.3%)	23 (76.7%)	48 (80.0%)	19 (100%)	18 (100%)	18 (100%)	10 (71.4%)	11 (68.8%)	13 (86.7%)	28 (96.6%)	30 (100.0%)	58 (98.3 %)	13 (100%)	11 (78.6%)	24 (88.9%)
Black or African American	5 (16.7%)	6 (20.0%)	11 (18.3%)				4 (28.6%)	3 (18.8%)	2 (13.3%)				0	2 (14.3%)	2 (7.4%)
Native Hawaiian or other Pacific Islander							0	1 (6.3%)	0						
Other	0	1 (3.3%)	1 (1.7%)				0	1 (6.3%)	0						
Asian										1 (3.4%)	0	1 (1.7%)			
Hispanic													0	1 (7.1%)	1 (3.7%)
Ethnicity															
Hispanic or Latino	12 (40.0%)	6 (20.0%)	18 (30.0%)	0	0	0	1 (7.1%)	2 (12.5%)	1 (6.7%)				13 (100%)	13 (92.9%)	26 (96.3%)
Not Hispanic or Latino	18 (60.0%)	24 (80.0%)	42 (70.0%)	19 (100%)	18 (100%)	18 (100%)	13 (92.9%)	14 (87.5%)	14 (93.3%)				0	1 (7.1%)	1 (3.7%)

The safety analysis sets for each study consisted of all randomized subjects who took at least 1 or partial dose of study medication (9785-CL-0010, 9785-CL-0003), who received any amount of study drug (9785-CL-0010), or who received at least 1 dose of study drug (MDV3100-05, 9785-CL-0014).

† Individual studies were described by different racial groupings. In this summary table, race for each study is summarized exactly as presented for that study in the Enzalutamide (MDV3100) Tablets (80 and 40 mg) CTD Module Summary of Clinical Safety. Shaded cells represent racial groups not presented for the particular study.

Max: maximum; Min: minimum; SD: Standard Deviation; Source: Enzalutamide (MDV3100) Tablets (80 and 40 mg) CTD Module 2.7.4 Summary of Clinical Safety, Tables 4 (MDV3100-05), 6 (9785-CL-0010), 8 (MDV3100-19), 10 (9785-CL-0014), and 12 (9785-CL-0003).

Data relevant to the safety of enzalutamide tablets were obtained from the 5 biopharmaceutic studies, 4 of which were single-dose studies involving a total of 220 healthy male subjects, and 1 of which was a multiple-dose study in 27 male patients with prostate cancer.

SIII.2 Clinical Trial Exposure

Five clinical studies relevant for the tablet formulation are described in [Section SIII.1]. Studies with enzalutamide have been conducted in prostate cancer patients with castrate levels of testosterone, hormone naïve patients and healthy male subjects. However, EMBARK included a treatment arm where enzalutamide monotherapy was administered in the absence of ADT and therefore the treatment did not lead to castrate levels of testosterone. No studies have been conducted in the pediatric population [Section SIV.3].

In this Risk Management Plan (RMP), the safety profile of enzalutamide in patients with either nmHSPC, mHSPC, nmCRPC or mCRPC is derived from 8 clinical studies involving 7678 unique patients. These studies include 1 randomized phase 3 study with two double-blind and one" open label arms in patients with nmHSPC with high-risk BCR after definitive therapy (MDV3100-13 [EMBARK]), 1 randomized, placebo-controlled phase 3 study in patients with mHSPC (9785-CL-0335 [ARCHES]), 1 randomized, placebo controlled phase 3 pivotal study in patients with nmCRPC (MDV3100-14 [PROSPER]), 2 randomized, placebo-controlled, phase 3 studies in chemotherapy-naïve patients with mCRPC (MDV3100-03 [PREVAIL] and 9785-CL-0232 [Asian PREVAIL]), 1 randomized, placebo-controlled, phase 3 study in patients with mCRPC previously treated with docetaxel-based chemotherapy (CRPC2 [AFFIRM], and 2 randomized, bicalutamide controlled, phase 2 studies in patients with mCRPC (9785-CL-0222 [TERRAIN]) and with nmCRPC or mCRPC (MDV3100 09 [STRIVE]). Of the 5110 enzalutamide-treated patients in the integrated safety population, 707 patients (13.8%) had nmHSPC, 752 patients (14.7%) had mHSPC and 3651 patients (71.4%) had CRPC. All patients in the integrated safety population also received medical or surgical ADT to maintain castrate levels of testosterone except for patients in the monotherapy arm in EMBARK.

The studies included in the integrated safety population are summarized in [Table SIII.3].

Table SIII.3 Completed and Ongoing Clinical Studies Included in this RMP

Study	Phase, Study Design	Population	Enz Dose (mg/day)	Number of Treated Patients				Safety Data Cutoff Date/Status
				Enz	Pbo	Bical	Total	
Controlled Double-Blind Studies in the Integrated Safety Population								
MDV3100-13 (EMBARK)	Phase 3. randomized DB and OL arms in parallel (efficacy and safety)	Patients with high-risk biochemical recurrence (BCR) nonmetastatic hormone-sensitive prostate cancer progressing after either radical prostatectomy or radiotherapy (nmHSPC)	160	353 (DB) 354 (OL)	354	NA	1061	31 Jan 2023/ Final analysis of MFS cutoff date
9785-CL-0335 (ARCHES)	Phase 3, randomized, double-blind, placebo-controlled (efficacy and safety)	Patients with metastatic hormone-sensitive prostate cancer (mHSPC)	160	572	574	NA	1146	28 May 2021/ Completed
MDV3100-14 (PROSPER)*	Phase 3, randomized, double-blind, placebo-controlled (efficacy, safety)	Patients with nonmetastatic CRPC	160	930	465	NA	1395	15 Oct 2019/Completed**
MDV3100-03 (PREVAIL)†	Phase 3, randomized, double-blind, placebo-controlled (efficacy, safety)	CN patients with asymptomatic or mildly symptomatic progressive metastatic CRPC	160	871	844	NA	1715	21 Mar 2019/Ongoing (open- label portion)
CRPC2 (AFFIRM)‡	Phase 3, randomized, double-blind, placebo-controlled (efficacy, safety, pharmacokinetics)	Patients with progressive metastatic CRPC previously treated with docetaxel-based chemotherapy	160	800	399	NA	1199	20 Feb 2018/ Completed
9785-CL-0232 (Asian PREVAIL) excluding site 105	Phase 3, randomized, double-blind, placebo-controlled (efficacy, safety, pharmacokinetics)	CN patients with progressive metastatic CRPC who failed ADT	160	202	193	NA	395	04 Nov 2020/ Ongoing (open-label portion)

9785-CL-0222 (TERRAIN)§	Phase 2, randomized, double-blind, bicalutamide-controlled (efficacy, safety)	CN patients with metastatic CRPC who failed ADT	160	183	NA	189	372	17 Feb 2018/Completed
MDV3100-09 (STRIVE)¶	Phase 2, randomized, double-blind, bicalutamide-controlled (efficacy, safety)	CN patients with metastatic or nonmetastatic CRPC who failed ADT	160	197[#]	NA	198[‡#]	395	30 May 2018/Completed
Total Patients in the Integrated Safety Population				**4462**	**2829**	**387**	**7678**	

ADT: Androgen Deprivation Therapy; Bical: Bicalutamide; BCR: Biochemical Recurrence; CN: Chemotherapy Naïve; CRPC: Castration-Resistant Prostate Cancer; DB: Double Blind; Enz: Enzalutamide; MFS: Metastasis Free Survival; mHSPC: Metastatic Hormone-Sensitive Prostate Cancer; NA: Not Applicable; OL: Open Label; Pbo: Placebo; RMP: Risk Management Plan.

*87 patients crossed over from placebo to enzalutamide treatment during the open-label extension. Open-label data are included in the exposure summaries and in the total enzalutamide pool.

** Final OS data has been completed in the CSR and only long-term safety follow up data will be continued.

† 234 patients crossed over from placebo to enzalutamide treatment during the open-label extension. Open-label data are included in the exposure summaries and in the total enzalutamide pool.

‡ 50 patients crossed over from placebo to enzalutamide treatment during the open-label extension. Open-label data are included in the exposure summaries and in the total enzalutamide pool.

§ 9 patients crossed over from bicalutamide to enzalutamide treatment during the open-label extension. Open-label data are included in the exposure summaries and in the total enzalutamide pool.

¶ 37 patients crossed over from bicalutamide to enzalutamide treatment during the open-label extension. Open-label data are included in the exposure summaries and in the total enzalutamide pool.

Includes 69 patients with nonmetastatic disease.

Source: Summary of Clinical Safety Table 2 and Table 14.1.1.1.

In the integrated safety population, 5110 patients (12585.63 PY) were exposed to enzalutamide, including 707 patients (3107.42 PY) with nmHSPC, 752 patients (1831.66 PY) with mHSPC, 2543 patients (4230.94 PY) with mCRPC and 1108 patients (3415.61 PY) with nmCRPC [Ad Hoc RMP Table 1.1]. The extent of exposure to enzalutamide in the integrated safety population for all indications and for nmHSPC, mHSPC, nmCRPC and mCRPC indications, presented as patient and person time (patient treatment-years), is summarized by duration [Table SIII.4], by age group and gender [Table SIII.5], by dose [Table SIII.6], by ethnic origin [Table SIII.7], and by baseline medical condition [Table SIII.8]. The dose of enzalutamide in all studies in the integrated safety population was 160 mg orally once daily. All treated patients in the integrated safety population were male.

Table SIII.4 Duration of Exposure

Cumulative for all Indications		
Duration of Exposure	**Patients**	**Person Time (Treatment-years)**
< 3 months	386	83.35
≥ 3 months to <6 months	478	210.73
≥ 6 months to <12 months	808	661.96
≥ 12 months to <24 months	1043	1567.26
≥ 24 months to <36 months	702	1834.4
≥ 36 months to <48 months	622	2368.86
≥ 48 months to <60 months	504	2419.72
≥ 60 months	567	3439.35
Total	**5110**	**12585.63**
Nonmetastatic CRPC		
Duration of Exposure	**Patients**	**Person Time (Treatment-years)**
< 3 months	38	7.20
≥ 3 months to <6 months	55	21.75
≥ 6 months to <12 months	94	76.65
≥ 12 months to <24 months	233	338.07
≥ 24 months to <36 months	222	654.6
≥ 36 months to <48 months	217	910.08
≥ 48 months to <60 months	180	968.65
≥ 60 months	69	438.61
Total for indication	**1108**	**3415.61**
Metastatic CRPC		
Duration of Exposure	**Patients**	**Person Time (Treatment-years)**
< 3 months	299	66.66
≥ 3 months to <6 months	371	166.45

≥ 6 months to <12 months	569	470.00
≥ 12 months to <24 months	619	916.88
≥ 24 months to <36 months	291	742.45
≥ 36 months to <48 months	141	503.97
≥ 48 months to <60 months	119	536.52
≥ 60 months	134	828.01
Total for indication	**2543**	**4230.94**
Metastatic HSPC		
Duration of exposure	**Patients**	**Person time (Treatment-years)**
< 3 months	33	6.11
≥ 3 months to <6 months	32	12.82
≥ 6 months to <12 months	72	59.19
≥ 12 months to <24 months	164	266.79
≥ 24 months to <36 months	145	323.29
≥ 36 months to <48 months	213	771.40
≥ 48 months to <60 months	93	392.06
≥ 60 months	0	0
Total for indication	**752**	**1831.66**
Nonmetastatic HSPC		
Duration of exposure	**Patients**	**Person time (Treatment-years)**
< 3 months	16	3.38
≥ 3 months to <6 months	20	9.71
≥ 6 months to <12 months	73	56.12
≥ 12 months to <24 months	27	45.51
≥ 24 months to <36 months	44	114.07
≥ 36 months to <48 months	51	183.41
≥ 48 months to <60 months	112	522.49
≥ 60 months	364	2172.74
Total for indication	**707**	**3107.42**

CRPC: Castration-Resistant Prostate Cancer.

HSPC: Hormone Sensitive Prostate Cancer Source: Ad Hoc RMP Table 1.1.

Table SIII.5 Exposure by Age Group and Gender

Cumulative for all Indications		
Age Group	**Patients**	**Person Time (Treatment-years)**
	Male	**Male**
< 65 years	1122	2629.92
65 – 74 years	2285	5819.08
75 – 84 years	1498	3724.39
> 84 years	205	412.24
Total	**5110**	**12585.63**
Nonmetastatic CRPC		
Age Group	**Patients**	**Person Time (Treatment-years)**
	Male	**Male**
< 65 years	150	460.24
65 – 74 years	425	1378.10
75 – 84 years	440	1348.99
> 84 years	93	228.29
Total for indication	**1108**	**3415.61**
Metastatic CRPC		
Age Group	**Patients**	**Person Time (Treatment-years)**
	Male	**Male**
< 65 years	615	950.74
65 – 74 years	1136	1897.51
75 – 84 years	705	1248.67
> 84 years	87	134.03
Total for indication	**2543**	**4230.94**
Metastatic HSPC		
Age Group	**Patients**	**Person Time (Treatment-years)**
	Male	**Male**
< 65 years	187	481.77
65 – 74 years	350	868.95
75 – 84 years	197	448.60
> 84 years	18	32.34
Total for indication	**752**	**1831.66**
Nonmetastatic HSPC		

Age Group	Patients	Person Time (Treatment-years)
	Male	Male
< 65 years	170	737.18
65 – 74 years	374	1674.53
75 – 84 years	156	678.13
> 84 years	7	17.57
Total for indication	**707**	**3107.42**

CRPC: Castration-Resistant Prostate Cancer. HSPC: Hormone Sensitive Prostate Cancer Source: Ad Hoc RMP Tables 1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5.

Table SIII.6 Exposure by Dose

Cumulative for all Indications		
Dose of Exposure	**Patients**	**Person Time (Treatment-years)**
160 mg daily	5110	12585.63
Total	5110	12585.63
Nonmetastatic CRPC		
Dose of Exposure	**Patients**	**Person Time (Treatment-years)**
160 mg daily	1108	3415.61
Total for indication	1108	3415.61
Metastatic CRPC		
Dose of Exposure	**Patients**	**Person Time (Treatment-years)**
160 mg daily	2543	4230.94
Total for indication	2543	4230.94
Metastatic HSPC		
Dose of Exposure	**Patients**	**Person Time (Treatment-years)**
160 mg daily	752	1831.66
Total for indication	752	1831.66
Nonmetastatic HSPC		
Dose of Exposure	**Patients**	**Person Time (Treatment-years)**
160 mg daily	707	3107.42
Total for indication	707	3107.42

CRPC: Castration-Resistant Prostate Cancer; HSPC: Hormone Sensitive Prostate Cancer
Source: Ad hoc RMP Tables 1.1

Table SIII.7 Exposure by Ethnic Origin

Cumulative for All Indications		
Ethnic Origin	**Patients**	**Person Time (Treatment-years)**
American Indian or Alaska native	6	18.21
Asian	710	1694.40
Black or African American	158	371.40
Native Hawaiian or other Pacific Islander	8	22.70
White	3932	9696.64
Multiple	16	51.32
Other	60	130.68
Unknown/missing	196	507.83
Not reported	24	92.44
Total for indication	**5110**	**12585.63**
Non Metastatic CRPC		
Ethnic Origin	**Patients**	**Person Time (Treatment-years)**
American Indian or Alaska native	0	0
Asian	158	437.29
Black or African American	39	115.08
Native Hawaiian or other Pacific	3	10.32
White	806	2503.66
Multiple	8	26.58
Other	11	40.41
Unknown/missing	83	282.28
Not reported	0	0
Total for indication	**1108**	**3415.61**
	Metastatic CRPC	
Ethnic Origin	**Patients**	**Person Time (Treatment-years)**
American Indian or Alaska native	2	1.00
Asian	388	753.34
Black or African American	76	119.60
Native Hawaiian or other Pacific	4	6.58
White	1939	3104.07
Multiple	2	0.97
Other	42	62.16
Unknown/missing	90	183.22
Not reported	0	0
Total for indication	**2543**	**4230.94**

Metastatic HSPC		
Ethnic Origin	**Patients**	**Person Time (Treatment-years)**
American Indian or Alaska native	0	0
Asian	112	275.20
Black or African American	12	29.68
Native Hawaiian or other Pacific Islander	0	0
White	602	1480.82
Multiple	0	0
Other	3	3.62
Unknown/missing	23	42.33
Not reported	0	0
Total for indication	**752**	**1831.66**
Nonmetastatic HSPC		
Ethnic Origin	**Patients**	**Person Time (Treatment-years)**
American Indian or Alaska native	4	17.21
Asian	52	228.57
Black or African American	31	107.04
Native Hawaiian or other Pacific Islander	1	5.80
White	585	2608.09
Multiple	6	23.77
Other	4	24.49
Unknown/missing	0	0
Not reported	24	92.44
Total for indication	**707**	**3107.42**

CRPC: Castration-Resistant Prostate Cancer. HSPC: Hormone Sensitive Prostate Cancer Source: Ad Hoc RMP Tables 1.2.1, 1.2.2, 1.2.4, 1.2.5.

Table SIII.8 Exposure by Baseline Medical Condition

Cumulative for all indications		
Baseline Medical Condition	**Patients[a]**	**Person Time (Treatment-years)**
History of cardiovascular disease	965	2407.89
History of hypertension	3050	7513.72
History of diabetes mellitus	1001	2420.48
History of hypercholesterolemia and/or hyperlipidemia	1559	4008.71
Total	**5110**	**12585.63**

Nonmetastatic CRPC		
Baseline Medical Condition	**Patients[a]**	**Person Time (Treatment-years)**
History of cardiovascular disease	229	713.65
History of hypertension	695	2090.55
History of diabetes mellitus	243	664.63
History of hypercholesterolemia and/or hyperlipidemia	342	1073.06
Total for indication	**1108**	**3415.61**
Metastatic CRPC		
Baseline Medical Condition	**Patients[a]**	**Person Time (Treatment-years)**
History of cardiovascular disease	464	826.51
History of hypertension	1492	2505.65
History of diabetes mellitus	469	807.77
History of hypercholesterolemia and/or hyperlipidemia	779	1333.86
Total for indication	**2543**	**4230.94**
Metastatic HSPC		
Baseline Medical Condition	**Patients[a]**	**Person Time (Treatment-years)**
History of cardiovascular disease	166	393.08
History of hypertension	437	1074.92
History of diabetes mellitus	156	365.31
History of hypercholesterolemia and/or hyperlipidemia	166	410.46
Total for indication	**752**	**1831.66**
Nonmetastatic HSPC		
Baseline Medical Condition	Patients[a]	Person Time (Treatment-years)
History of cardiovascular disease	106	474.65
History of hypertension	426	1842.6
History of diabetes mellitus	133	582.77
History of hypercholesterolemia and/or hyperlipidemia	272	1191.32
Total for indication	**707**	**3107.42**

CRPC: Castration-Resistant Prostate Cancer. HSPC: Hormone Sensitive Prostate Cancer Source: Ad Hoc RMP Tables 1.2.1, 1.2.2, 1.2.4, 1.2.5.

a: A single patient might report more than one baseline medical condition.

PART II: MODULE SIV. POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

The majority of the exclusion criteria were established in order not to confound the assessment of safety and efficacy or to prevent enrollment of subjects with conditions for whom participation in a clinical trial would not be in their best interest. Important exclusion criteria in the clinical development program are discussed in [Table SIV.1].

Table SIV.1 Important exclusion criteria pivotal clinical trials across the development program

Criterion 1	**History of seizure, loss of consciousness or transient ischemic attack within (12 months of randomization), or any condition that may predispose to seizure (e.g., stroke, brain arteriovenous malformation, head trauma, underlying brain injury)**
Reason for being an exclusion criterion	These exclusion criteria were applied to the 8 clinical studies comprising the integrated safety population and were related to the higher risk of seizure in these patients and based on nonclinical information and previous experience with the use of enzalutamide in humans (seizure is a known important identified risk and an expected adverse drug reaction).
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	The risk of seizure in enzalutamide-treated patients with predisposing factors for seizure was evaluated in a postauthorization safety study (single-arm phase 4 trial 9785-CL-0403).
Criterion 2	**Known or suspected brain metastases or active epidural/leptomeningeal disease**
Reason for being an exclusion criterion	This exclusion criterion was applied to the 8 clinical studies comprising the integrated safety population and was related to the higher risk of seizure in these patients and based on nonclinical information and previous experience with the use of enzalutamide in humans (seizure is a known important identified risk and an expected adverse drug reaction).
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	The risk of seizure in enzalutamide-treated patients with predisposing factors for seizure, including patients with brain metastases or primary brain tumor, was evaluated in a postauthorization safety study (single-arm phase 4 trial 9785-CL-0403).
Criterion 3	**Use of concomitant medications that lower the seizure threshold**
Reason for being an exclusion criterion	This exclusion criterion was applied to Study CRPC2 and was related to the higher risk of seizure in patients receiving concomitant medications that lower the seizure threshold and based on nonclinical information and previous experience with the use of enzalutamide in humans (seizure is a known important identified risk and an expected adverse drug reaction).
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	The risk of seizure in enzalutamide-treated patients with predisposing factors for seizure, including patients using medication that may lower

	seizure threshold, was evaluated in a postauthorization safety study (single-arm phase 4 trial 9785-CL-0403).
Criterion 4	**Laboratory assessments for hepatic function (T-Bil, ALT, or AST > approximately 2 times the ULN)**
Reason for being an exclusion criterion	This exclusion criterion was applied to the 8 clinical studies comprising the integrated safety population, and was a precaution taken in order to prevent the exposure of patients with severe preexisting medical conditions to an investigational drug.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	Currently available data support the assessment that there is no evidence of direct or dose-related hepatotoxicity associated with enzalutamide. No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment. The pharmacokinetics of enzalutamide were examined in subjects with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) and in matched control subjects with normal hepatic function [9785-CL-0009, 9785-CL-0404]. Hepatic impairment did not have a pronounced effect on the total exposure to enzalutamide or its active metabolite. The results of these studies show that no dose adjustment of enzalutamide is required for patients with mild, moderate, or severe hepatic impairment.
Criterion 5	**Laboratory assessment for renal function (creatinine > 177 µmol/L [2 mg/dL])**
Reason for being an exclusion criterion	This exclusion criterion was applied to the 8 clinical studies comprising the integrated safety population and was a precaution in order to prevent the exposure of patients with severe preexisting medical conditions to an investigational drug for which there was insufficient safety information at the time of the conduct of the studies.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	Renal impairment most often occurs as a consequence of disease progression in CRPC patients and is due to a mechanical obstruction from tumor burden. Disease progression in most cases eventually leads to permanent discontinuation of enzalutamide. Therefore, it is challenging to further assess the safety profile of the drug in patients with severe renal impairment. Given that enzalutamide is mainly metabolized via the liver, there is no expectation for a different safety profile in patients with severe renal impairment. Appropriate risk minimization for patients with severe renal impairment is provided in the SmPC and PL.
Criterion 6	**Significant cardiovascular disease (recent MI or unstable angina, NYHA class III or IV heart failure [except if LVEF ≥ 45%], history of clinically significant ventricular arrhythmias [e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes], history of Mobitz II second degree or third degree heart block without a permanent pacemaker in place, hypotension [SBP < 86 mm Hg], bradycardia [HR < 50 bpm], uncontrolled hypertension [SBP > 170 mm Hg or DBP > 105 mm Hg])**
Reason for being an exclusion criterion	This exclusion criterion was applied to the 8 clinical studies comprising the integrated safety population and was a precaution in order to prevent the exposure of patients with severe pre-existing medical conditions to an investigational drug for which there was insufficient safety information at the time of the conduct of the studies.
Is it considered to be included as missing information?	No

Rationale (if not included as missing information)	Inclusion of patients with severe cardiovascular disease in the upcoming studies is not planned. The feasibility of successfully studying the safety profile of enzalutamide in patients with severe cardiovascular disease is low owing to several design features such as confounding factors, poly therapy, etc., especially in view of ascertaining causal attribution as the primary endpoint. Appropriate risk minimization for patients with severe cardiovascular disease is provided in the SmPC and PL.
Criterion 7	**Use of concomitant medications that prolong the QT interval**
Reason for being an exclusion criterion	The concomitant QT interval prolonging medication was used as standard exclusion criteria for a phase 3 study with an ECG assessment embedded in the study (CRPC2). This criterion was used to increase the scientific robustness of the study and not primarily introduced for safety reasons.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	This criterion was applied to Study CRPC2, but not to MDV3100-03. MDV3100-09, MDV3100-14, 9785-CL-0222, and 9785-CL-0232. The results of the ECGs review from an embedded ECG assessment sub study in Study CRPC2 did not suggest a clinically important effect of enzalutamide on QT interval.
Criterion 8	**Pregnancy/nursing mothers**
Reason for being an exclusion criterion	Due to the nature of the disease (Prostate cancer), women were not enrolled in the 8 clinical studies comprising the integrated safety population. There are currently no safety or efficacy data to support the use of enzalutamide during pregnancy/breast-feeding. Nonclinical studies showed that enzalutamide treatment of pregnant mice resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes. Enzalutamide may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	There is a potential mechanistic-basis for effects on reproduction/fertility. Given the nature of the patient population treated with enzalutamide (elderly men with castrate levels of testosterone) and the lack of an approved indication in female patients, further investigation of enzalutamide effect on reproduction/fertility is not planned. No clinical trials in female patients are planned at this time. Appropriate risk minimization language (therapeutic indication in adult men, contraindication in women who are or may become pregnant, and recommendations for effective contraception in male and female partners of patients treated with enzalutamide) is provided in the SmPC and PL.
Criterion 9	**Patients with ECOG performance status ≥ 2**
Reason for being an exclusion criterion	Only patients with ECOG performance status of 0 or 1 were included in Studies MDV3100-03, MDV3100-09, MDV3100-14, 9785-CL-0222, 9785-CL-0232 and MDV3100-13. Patients with ECOG performance status of 0, 1, or 2 were enrolled in CRPC2. Patients with advanced disease were excluded from clinical trials due to their potential increased vulnerability to an investigational agent.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	As of the DLP for this Module (15 Oct 2019), the MAH has not received reports of decreased efficacy of enzalutamide in patients with ECOG performance status ≥ 2, and there is no expectation for a different safety

	profile in these patients. There is no data indicating that dose adjustment is required for patients with ECOG performance status ≥ 2.
Criterion 10	**Metastatic CRPC patients previously treated with abiraterone**
Reason for being an exclusion criterion	Patients previously treated with abiraterone were excluded from Studies MDV3100-09, MDV3100-14, and 9785-CL-0232 due to lack of evidence that enzalutamide is effective following treatment with abiraterone.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	The use of enzalutamide in metastatic CRPC patients previously treated with abiraterone acetate was evaluated in a single-arm phase 4 postauthorization efficacy and safety study 9785-CL-0410.

ALT: Alanine Transaminase; AST: Aspartate Transaminase; CRPC: Castration-Resistant Prostate Cancer; DBP: Diastolic Blood Pressure; DLP: Data Lock Point; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; MAH: Marketing Authorization Holder; MI: Myocardial Infarction; NYHA: New York Heart Association; PL: Package Leaflet; SBP: Systolic Blood Pressure; SmPC: Summary of Product Characteristics; T-Bil: Total Bilirubin; ULN: Upper Limit Of Normal.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program for enzalutamide is unlikely to detect certain types of adverse reactions such as rare adverse reactions (i.e., occurring < 1/1000 patients).

In the integrated safety population of 5110 enzalutamide-treated patients, 3438 patients were treated for ≥ 12 months, with a maximum duration of 95 months (ISS table 14.1.6.1). The extent of exposure to enzalutamide in the clinical program, with substantial numbers of patients across different age categories, races, geographic regions and baseline cardiovascular risk status, was sufficient to adequately characterize the safety profile of enzalutamide in patients with CRPC and HSPC. Due to the extent of exposure in the clinical trials population treated by enzalutamide, adverse reactions due to prolonged or cumulative exposure and adverse reactions with a long latency should have been detected in this population.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.2: Exposure of special populations included or not in clinical trial development programs

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant women</td><td rowspan="2">Not included in the clinical development program</td></tr>
<tr><td>Breastfeeding women</td></tr>
<tr><td>• Patients with relevant comorbidities:</td><td></td></tr>
<tr><td>• Patients with hepatic impairment</td><td>Sufficient hepatic function was required for a patient with prostate cancer to be considered eligible for enrollment in an enzalutamide study. For the studies included in the integrated safety population, T-Bil, ALT or AST > approximately 2 times the ULN at the screening visit was applied as exclusion criteria.
The pharmacokinetics of enzalutamide following a single oral 160 mg dose of enzalutamide were examined in subjects with baseline mild (n = 6), moderate (n = 8), or severe (n=8) hepatic impairment (Child-Pugh Class A, B, or C, respectively) and in 22 matched control subjects with normal hepatic function.
Plasma exposure in subjects with hepatic impairment (mild, moderate, severe) compared to healthy control subjects
<table>
<tr><th>Hepatic impairment</th><th colspan="2">Enzalutamide</th><th colspan="2">Unbound enzalutamide + unbound active metabolite</th></tr>
<tr><th></th><th>AUC</th><th>C_{max}</th><th>AUC</th><th>C_{max}</th></tr>
<tr><td>Mild</td><td>↑5%</td><td>↑24%</td><td>↑14%</td><td>↑19%</td></tr>
<tr><td>Moderate</td><td>↑29%</td><td>↓11%</td><td>↑14%</td><td>↓17%</td></tr>
<tr><td>Severe</td><td>↑5%</td><td>↓42%</td><td>↑34%</td><td>↓27%</td></tr>
</table>
An increased drug half-life was observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. As stated in the SmPC, no dose adjustment is necessary for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively).</td></tr>
<tr><td>• Patients with renal impairment</td><td>Only patients with a mild to moderate renal impairment were allowed in the enzalutamide studies. No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with mild to moderate renal impairment (calculated CRCL values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CRCL < 30 mL/min) or end-stage renal disease, and, as stated in the SmPC, caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent hemodialysis or continuous ambulatory peritoneal dialysis.</td></tr>
<tr><td>• Patients with cardiovascular impairment</td><td>The studies comprising the integrated safety population excluded patients with recent MI (in the past 6 months) or unstable angina (in the past 3 months), NYHA III or IV heart failure except if LVEF ≥ 45%, bradycardia, or uncontrolled hypertension; this should be taken into account if enzalutamide is prescribed in these patients. Of the 5110 enzalutamide- treated patients in the integrated safety population, 965 (18.88%) had a history of cardiovascular disease that did not meet the exclusion criteria described in [Table SIV.1] [Source Ad Hoc RMP Table 1.2.4].</td></tr>
</table>

Type of special population	Exposure
• Patients with a disease severity different from inclusion criteria in clinical trials	Two exclusion criteria were applied that relate to disease severity: • ECOG performance status; • Brain metastases. Patients with ECOG performance status 3 or 4 were not eligible for the enzalutamide studies. Patients with ECOG performance status 2 to 4 were not eligible for enrollment in 7 of the 8 studies comprising the integrated safety population (9785-CL-0335, MDV3100-03, MDV3100-09, MDV3100-14, 9785-CL-0222, 9785-CL-0232 and MDV3100-13). The ECOG performance status is generally related to the severity of the underlying disease; however, it is not a specific indicator and could be affected by other factors (e.g., comorbidity, side effects of medication, etc.). All patients enrolled in the clinical trials comprising the integrated safety population had ECOG performance status 0 to 3, predominantly grade 0 or 1. The safety, tolerability and efficacy of enzalutamide have not been evaluated in patients with ECOG performance status 3 or 4 and are therefore unknown. As per protocol, patients with known brain metastases or active epidural disease were ineligible for enrollment in the enzalutamide studies due to increased risk of seizure. However, patients with brain metastases were included in 9785-CL- 0403 study, a single-arm, open-label, postmarketing safety study that evaluated the risk of seizure in metastatic CRPC subjects with predisposing factors for seizure.
Population with relevant different ethnic origin	There were no restrictions for enrollment regarding race and/or ethnicity in the clinical studies comprising the integrated safety population. Of the 5110 enzalutamide-treated patients in the integrated safety population, 3932 (76.9%) were White, 158 (3.1%) were Black, 710 (13.9%) were Asian, 8 (0.2%) were Native Hawaiian or other Pacific Islander, 6 (0.1%) were American Indian or Alaska native, and 76 (1.5%) subjects were of other, multiple races. In 220 (4.3%), race was unknown or was not reported. [Source: Ad Hoc RMP Table 1.2.4]. The low number of enrolled patients in the non- White/Hispanic/Latino ethnic/racial groups could reduce the generalizability of the efficacy and safety of enzalutamide in populations other than White. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Whites. There were insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations of subjects with genetic polymorphisms were not identified in the development program and hence no data exists. Based on the low inter-subject variability in pharmacokinetic parameters, and the approximate normal (or symmetric) distribution of steady state, enzalutamide C_{min} values in the pivotal phase 3 Studies CRPC2 and MDV3100-03, there do not appear to be subpopulations of phenotypic poor metabolizers.
Children and adolescents < 18 years of age	There have been no studies conducted with enzalutamide in the pediatric population, as the main indication is limited to prostate cancer, for which there is a class-waiver from the need to perform pediatric studies. Enzalutamide is not recommended for use in children and adolescents due to lack of data on safety and efficacy. As stated in the SmPC, there is no relevant use of enzalutamide in the pediatric population in the indication of treatment of adult men with CRPC.
Elderly	No upper limit of age was applied during the development program of enzalutamide. Patients 65 to 74 years-old and ≥ 75 years-old were well represented in the integrated safety population, with 44.7% and 33.3% of the patients on enzalutamide, respectively [Source: Ad Hoc RMP Table 1.2.4].

ALT: Alanine Transaminase; AST: Aspartate Transaminase; AUC: Area Under The Plasma Concentration-Time Curve; Cmax: Maximum Drug Concentration; CRCL: Creatinine Clearance; CRPC: Castration-Resistant Prostate Cancer; ECOG: Eastern Cooperative Oncology Group; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; NYHA: New York Heart Association; RMP: Risk management Plan; SmPC: Summary of Product Characteristics; T-Bil: Total Bilirubin; ULN: Upper Limit Of Normal.

PART II: MODULE SV. POSTAUTHORIZATION EXPERIENCE

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

SV.1 Postauthorization exposure

SV.1.1 Method used to calculate exposure

The enzalutamide postmarketing exposure estimates are based on internal sales data for all countries. These internal sales data represent product shipment from manufacturer to distributor (i.e., wholesaler, specialty pharmacy, etc.), and do not include sales direct to patient, free product, or product samples. The initial sales of the product represent distributor stocking of the product. This may thus result in an overestimate of patient exposure following initial launch. The methodology for calculating the number of patients may vary due to the amount of data available and the duration of market exposure in the respective regions.

Enzalutamide is distributed in bottles and packages that approximate 1 month of treatment. The number of bottles and packages distributed was divided by 12 in order to estimate patient treatment years with enzalutamide.

Patient demographic information is available in the US, Europe (France, Germany, Italy, Spain, and United Kingdom), and Japan. The gender and age of patients who received enzalutamide are based on the IPSOS Tandem Cancer Audit Program, which captures product usage based on patient records completed by medical oncologists, hematologist/ oncologists, gynecologic oncologists, hematologists, pediatric hematologist/oncologists, urologists and internists with a secondary specialty in oncology. IPSOS developed a proprietary methodology that projects from a sample size to the total population universe. The panel size is approximately 500 physicians with approximately 450 unique sites.

The allocation factors are derived from the cumulative number of patients treated with enzalutamide in the US, Japan, and Europe.

SV.1.2 Exposure

The cumulative exposure from Sep 2012 up to 31 Jan 2023 is estimated to be 829 136 patient treatment years [Table SV.1].

Table SV.1 Postauthorization Exposure from Marketing Experience by Region

Region	Person-time (patient treatment years)
Total America	**261 366**
United States	[redacted]
United States Patient Assistance Program	[redacted]
Canada	[redacted]
Latin America	[redacted]
Europe	**322 826**

Total Asia	**244 944**
Japan	[redacted]
Asia	[redacted]
Total	**829 136**

Allocation by gender in the US, Europe, and Japan is provided in [Table SV.2].

Table SV.2 Gender Allocation in the United States, Europe, and Japan

Gender	Percentage of Total Patients		
	United States	**Europe**	**Japan**
Male†	100%	100%	100%

† Enzalutamide is approved for treatment of patients with metastatic CRPC and for patients with metastatic CRPC who previously received docetaxel. Enzalutamide is not approved for use in females. CRPC: castration-resistant prostate cancer

There are no data available regarding patient exposure from marketing experience based on racial group distribution.

PART II: MODULE SVI. ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Data-lock point for this Module	30 Aug 2018
Version when Module last updated	12.5

Potential for misuse for illegal purposes

There is no nonclinical or clinical evidence that enzalutamide has potential for drug abuse, and specific clinical studies evaluating for misuse potential have not been conducted.

The indication, complexity of synthetic pathway, poor solubility, inability to be administered parenterally and absence of large variation between minimum and maximum plasma concentration make it unlikely that enzalutamide has abuse potential. Additionally, in clinical studies, there were no signals suggestive of abuse such as increased incidence of events of euphoria, excessive use of study drug, and refusal to return unused study drug after study termination.

Despite limited data, no cases of enzalutamide misuse since authorization have been reported.

PART II: MODULE SVII. IDENTIFIED AND POTENTIAL RISKS

Data-lock point for this Module	The data lock point for postmarketing adverse event data is 31 Jan 2023. The data lock point for epidemiology and relevant literature within this Module is 31 Jan 2023. The data lock point for 9785-CL-0335 (ARCHES) is 28 May 2021. The data lock point for MDV3100-14 (PROSPER) is 15 Oct 2019. The data lock points for the other phase 3 studies are 21 Mar 2019, 20 Feb 2018 and 04 Nov 2020 for MDV3100-03, CRPC2 and 9785-CL-0232, respectively. The data lock points for the phase 2 studies are 17 Feb 2018 and 30 May 2018 for 9785-CL-0222 and MDV3100-09, respectively. The data lock point for MDV3100-13 (EMBARK) is 31 Jan 2023.
Version when Module last updated	18.0

SVII.1 Identification of safety concerns in the initial RMP submission

Section SVII.1 is not applicable, as this RMP is not an initial RMP submission.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not Applicable

SVII.1.2 Risk considered important for inclusion in the list of safety concerns in the RMP

Not Applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns in this updated RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII3.1 Presentation of important identified risks and important potential risks

In this section, safety information is included from the following sources (refer to [Module SIII] for a summary of the individual studies):

MDV3100-13 (EMBARK)	Safety data from a phase 3, randomized, efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in men with high-risk nonmetastatic prostate cancer progressing after definitive therapy, comprising safety populations of 353 enzalutamide + leuprolide-treated patients, 354 enzalutamide monotherapy treated patients and 354 patients in the placebo plus leuprolide group. This study was ongoing, as of the data lock point 31 Jan 2023. Treatment groups: enzalutamide + Leuprolide, placebo + leuprolide, enzalutamide monotherapy.
9785-CL-0335 (ARCHES)	Safety data from the randomized, placebo-controlled, phase 3 pivotal study in patients with metastatic HSPC [9785-CL-0335], comprising safety populations of 572 enzalutamide-treated patients and 574 patients in the placebo group, which supports the indication in metastatic HSPC. This study was ongoing, as of the data lock point 28 May 2021. Treatment groups: enzalutamide, placebo.
MDV3100-14 (PROSPER)	Safety data from the randomized, placebo-controlled, phase 3 pivotal study (MDV3100-14, PROSPER) in patients with nmCRPC at high risk of disease progression based on rising PSA levels and sufficiently short (≤ 10-month) Prostate-Specific Antigen Doubling Time (PSADT) comprising safety data of 930 enzalutamide-treated patients and 465 in the placebo group, which supports the indication in nmCRPC. This study was ongoing, as of the data cutoff date for this study of 15 Oct 2019. Treatment groups: enzalutamide, placebo.
Phase 3 Studies	This combined controlled population includes safety data from 4 phase 3, randomized, placebo-controlled studies in patients with nmCRPC and mCRPC (MDV3100-14, MDV3100-03, CRPC2 and 9785-CL-0232), data from the ARCHES (9785-CL-0335) study in mHSPC, and data from the EMBARK (MDV3100-13) study in nmHSPC, comprising a total of 3728 enzalutamide-treated patients and 2829 in the placebo group. These studies included patients with nmCRPC, and those with more advanced mCRPC previously treated with docetaxel and patients with mCRPC not previously treated with docetaxel who were considered chemotherapy-naïve. The data cutoff dates for the phase 3 studies were 28 May 2021, 15 Oct 2019, 21 Mar 2019, 20 Feb 2018, 04 Nov 2020, and 31 Jan 2023 for 9785-CL-0335, MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232 and MDV3100-13, respectively. As of the data cutoff dates, CRPC2 had completed, and MDV3100-14 and the open- label portions of the other 2 studies were ongoing. Treatment groups: enzalutamide, placebo.
Phase 2 Studies	This combined controlled population includes safety data from 2 phase 2, bicalutamide-controlled studies in patients with nmCRPC and mCRPC (9785-CL-0222 and MDV3100-09), comprising 380 enzalutamide-treated patients and 387 bicalutamide- treated patients. The data cutoff dates for the phase 2 studies were 17 Feb 2018 and 30 May 2018 for 9785-CL-0222 and MDV3100-09, respectively. As of the data cutoff dates, both studies had completed. Treatment groups: enzalutamide, bicalutamide.
Total Enzalutamide	The total enzalutamide group consists of all enzalutamide-treated patients from the 8 studies mentioned above (9785-CL-0335, MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785-CL-0222, MDV3100-09 and MDV3100-13), comprising of 5110 patients with mHSPC, nmCRPC, mCRPC and nmHSPC. Treatment group: enzalutamide.

For more information on the individual studies, please refer to [Module SIII].

The incidence proportions (%) presented in this section are calculated as number of patients with at least 1 event divided by the total number of patients exposed.

Time-adjusted rate per 100 PY rates were calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group multiplied by 100. Patients can have more than one occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

Time-adjusted rate per 100 PY rates were calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group multiplied by 100. Patients can have more than one occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

Important Identified Risk: Seizure

Potential mechanisms:

Enzalutamide and its active metabolite M2 showed significant off-target interaction with the rat gamma aminobutyric acid (GABA)-gated chloride channel (enzalutamide half maximal inhibitory concentration [IC_{50}] = 2.6 μM). Since both enzalutamide and M2 functionally inhibited the GABA-gated chloride channel (α1β3 and α1β3γ2 GABA-A receptor subtype) in a cell-based activity assay, additional studies were performed to assess convulsion potential in mice. Enzalutamide treatment was associated with dose-dependent convulsions in mice. Convulsions were frequent after multiple doses at 200 mg/kg and single doses at 400 mg/kg but were not observed after multiple doses at 60 mg/kg/day or single doses at 100 mg/kg. Plasma exposure to enzalutamide for the lowest dose that was associated with convulsions in mice (200 mg/kg) was at least 3.3 times higher than the mean exposure in patients receiving the clinical dose of 160 mg/day. Both enzalutamide and M2 were shown to cross the blood-brain barrier. A publication by Foster and colleagues showed that $GABA_A$-mediated convulsion was identified as a common off-target effect of a series of second-generation androgen receptor antagonists. In this report, enzalutamide was shown to cause dose-dependent convulsions in mice, with 4 out of 5 animals showing convulsions after days of dosing of 200 mg/kg. Comparison of brain concentrations of these compounds in mice, with and without convulsions, showed that seizurogenic activity is mainly dependent on the extent of brain penetration [Foster et al, 2011].

Evidence sources and strength of evidence:

This important identified risk is based on data from enzalutamide toxicology studies in animals and clinical studies. Seizures were observed in animals in nonclinical toxicology studies (1 rat and 2 dogs) administered enzalutamide, and there was a dose-dependent increase of seizures in mice. The event of seizure is an uncommon adverse drug reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of seizure was 1.1% in the enzalutamide + ADT group as compared to 0.8% in the enzalutamide monotherapy group. There was no incidence of seizure in placebo + ADT group. In 9785-CL-0335 (ARCHES) in mHSPC patients, the incidence of the event of seizure was lower in the enzalutamide group compared with the placebo group (0.3% vs. 0.5%). In MDV3100- 14 (PROSPER), the incidence of seizure was low in both groups, but numerically higher in the enzalutamide group compared with the placebo group (0.3% vs

0%) in the double-blind portion of the study. In the phase 3 studies in patients with mHSPC and with nmCRPC and mCRPC, the incidence of any event of seizures was 0.4% in the enzalutamide group compared with 0.1% in the placebo group. From the pooled phase 3 studies and phase 2 studies, the incidence of seizures among the enzalutamide treated patients in the double-blind plus open label group was 0.6%. When adjusted for duration of exposure, the event rates of seizure remained higher in the enzalutamide-treated groups compared with the placebo groups for the phase 3 studies but not for Study 9785-CL-0335 (ARCHES).

Characterization of the risk:

Frequencies and time-adjusted event rates for treatment-emergent adverse events (TEAEs) of seizures, as defined by the Convulsions standardized MedDRA query (SMQ) (narrow), are summarized in [Table SVII.1] for MDV3100-13 (EMBARK), phase 3 studies and total enzalutamide, by preferred term (PT), seriousness, action taken with study drug, severity, and timing of the event.

Review of postmarketing data for this important identified risk of Seizure was consistent with findings in the clinical trial database. No new safety information pertaining to this risk emerged from postmarketing experience.

Table SVII.1 Treatment-emergent Adverse Events of Seizures as Defined by the Narrow SMQ of Convulsions

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Convulsions - Overall	4 (1.1%)	0	3 (0.8%)	16 (0.4%)	4 (0.1%)	31 (0.6%)
Within the first 30 days	0/353	0/354	0/354	2/3728 (0.1%)	1/2829 (0.0%)	2/5110 (0.0%)
Between 31 to 180 days	1/353 (0.3%)	0/353	0/354	6/3720 (0.2%)	0/2816	9/5098 (0.2%)
Between 181 to 365 days	0/336	0/344	0/345	3/3200 (0.1%)	1/1796 (0.1%)	6/4389 (0.1%)
Between 366 to 540 days	0/285	0/306	0/313	0/2554	2/1183 (0.2%)	0/3530
Between 541 to 730 days	0/285	0/293	0/305	2/2027 (0.1%)	0/735	3/2880 (0.1%)
Between 731 to 900 days (2.5 years)	0/280	0/272	1/293 (0.3%)	0/1521	0/425	2/2414 (0.1%)
between 2.5 to 3 Years	1/270 (0.4%)	0/ 255	0/ 285	1/1116 (0.1%)	0/333	2/2081 (0.1%)
between 3 to 4 Years	1/260 (0.4%)	0/ 238	1/ 268 (0.4%)	1/785(0.1%)	0/265	3/1790 (0.2%)
between 4 to 5 Years	1/244(0.4%)	0/ 205	1/ 238 (0.4%)	1/ 504(0.2%)	0/207	3/1247 (0.2%)
between 5 to 6 Years	0/185	0/145	0/ 179	0/ 272	0/145	0/737
>6 Years	0/84	0/ 63	0/ 81	0/ 99	0/63	1/328 (0.3%)
Convulsions Leading to Study Drug Discontinuation [3,4]	2 (0.6%)	0	2 (0.6%)	10 (0.3%)	3 (0.1%)	20 (0.4%)
Convulsions Leading to Dose Interruption[4]	0	0	1 (0.3%)	1 (0.0%)	0	3 (0.1%)
Convulsions Leading to Dose Reduction[4]	0	0	0	0	0	0
Convulsions Leading to Death	0	0	0	0	0	0
Serious Convulsions	4 (1.1%)	0	2 (0.6%)	16 (0.4%)	4 (0.1%)	28 (0.5%)
Grade 3 or Higher Convulsions	2 (0.6%)	0	2 (0.6%)	12 (0.3%)	2 (0.1%)	18 (0.4%)
Within the first 30 days	0/353	0/354	0/354	2/3728 (0.1%)	1/2829 (0.0%)	2/5110 (0.0%)
Between 31 to 180 days	0/353	0/353	0/354	4/3720 (0.1%)	0/2816	5/5098 (0.1%)
Between 181 to 365 days	0/336	0/344	0/345	3/3200 (0.1%)	1/1796 (0.1%)	3/4389 (0.1%)
Between 366 to 540 days	0/285	0/306	0/313	0/2554	0/1183	0/3530
Between 541 to 730 days	0/285	0/293	0/305	1/2027 (0.0%)	0/735	1/2880 (0.0%)
Between 731 to 900 days (2.5 years)	0/280	0/272	0/293	0/1521	0/425	0/2414
between 2.5 to 3 Years	1/270 (0.4%)	0/255	0/285	1/1116 (0.1%)	0/333	2/2081 (0.1%)
between 3 to 4 Years	1/260 (0.4%)	0/238	1/268 (0.4%)	1/ 785 (0.1%)	0/265	2/1790 (0.1%)
between 4 to 5 Years	0/244	0/205	1/238 (0.4%)	0/504	0/207	2/1247 (0.2%)
between 5 to 6 Years	0/185	0/145	0/179	0/272	0/145	0/737
>6 Years	0/84	0/63	0/81	0/ 99	0/63	1/328 (0.3%)
Drug-Related[5] Convulsions	2 (0.6%)	0	2 (0.6%)	10 (0.3%)	2 (0.1%)	19 (0.4%)

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Grade 3 or Higher Drug-Related[5] Convulsions	1 (0.3%)	0	2 (0.6%)	7 (0.2%)	1 (0.0%)	9 (0.2%)
Drug-Related[5] Serious Convulsions	2 (0.6%)	0	2 (0.6%)	10 (0.3%)	2 (0.1%)	17 (0.3%)
Grade 3 or 4 Convulsions	2 (0.6%)	0	2 (0.6%)	12 (0.3%)	2 (0.1%)	18 (0.4%)
Within the first 30 days	0/353	0/354	0/354	2/3728 (0.1%)	1/2829 (0.0%)	2/5110 (0.0%)
Between 31 to 180 days	0/353	0/353	0/354	4/3720 (0.1%)	0/2816	5/5098 (0.1%)
Between 181 to 365 days	0/336	0/344	0/345	3/3200 (0.1%)	1/1796 (0.1%)	3/4389 (0.1%)
Between 366 to 540 days	0/285	0/306	0/313	0/2554	0/1183	0/3530
Between 541 to 730 days	0/285	0/293	0/305	1/2027 (0.0%)	0/735	1/2880 (0.0%)
Between 731 to 900 days (2.5 years)	0/280	0/272	0/293	0/1521	0/425	0/2414
between 2.5 to 3 Years	1/270 (0.4%)	0/255	0/285	1/1116 (0.1%)	0/333	2/2081 (0.1%)
between 3 to 4 Years	1/260 (0.4%)	0/238	1/268 (0.4%)	1/ 785 (0.1%)	0/265	2/1790 (0.1%)
between 4 to 5 Years	0/244	0/205	1/238 (0.4%)	0/504	0/207	2/1247 (0.2%)
between 5 to 6 Years	0/185	0/145	0/179	0/272	0/145	0/737
>6 Years	0/84	0/63	0/ 81	0/ 99	0/63	1/328 (0.3%)

[1] Phase 3 studies include MDV3100-13 (ENZA+ADT and PBO+ADT arms), DB phase for MDV3100-14, 9785-CL-0335, CRPC2, MDV3100-03, and 9785-CL-0232.

[2] Phase2/3 enzalutamide include all enzalutamide-treated subjects during DB and/or OL period of MDV3100-13 (ENZA+ADT and ENZA Mono arms), MDV3100-14, 9785-CL-0335, CRPC2, MDV3100-03, 9785-CL-0232, 9785-CL-0222, and MDV3100-09.

[3] Convulsions leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

[4] It could be related to any study drug (enzalutamide and/or leuprolide, placebo).

[5] Drug-Related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug. NCI-CTCAE Version 4.03.

Note: Number of patients reporting at least one event of Convulsions and percentage of these patients (%) are shown.

ADT: Androgen Deprivation Therapy; DB: Double-blind; ENZA: Enzalutamide; nmCSPC: Nonmetastatic Castration-Sensitive Prostate Cancer; OL: Open-label; PBO: Placebo.

Note: Nonmetastatic castration sensitive prostate cancer (nmCSPC) has been captured as per the ISS table which is equivalent to the indication nonmetastatic hormone sensitive prostate cancer (nmHSPC), proposed in the EMBARK study.

Cut-off: MDV3100-13:31JAN2023, MDV3100-14:15OCT2019, 9785-CL-0335:28MAY2021, CRPC2:20FEB2018, MDV3100-03:21MAR2019, 9785-CL-0232:04NOV2020, 9785-CL-0222:17FEB2018, MDV3100-09:30MAY2018.

Risk factors and risk groups:

Risk Factor/Group	Description
Dose	Nonclinical and clinical data. A dose-response relationship between enzalutamide and seizure was suggested in a dose escalation study.
Predisposing factors for seizure	Seizure event rate among enzalutamide-treatment mCRPC patients who were potentially at an increased risk of seizure was 1.1% (Study 9785-CL-0403). This was comparable with the seizure rate in the other studies, despite the inclusion of patients with potential risk factors for seizure.
Metastatic disease (CNS)	In a retrospective cohort study, the incidence of seizure in mCRPC patients was higher in patients with at least 1 risk factor than in those with no risk factors, with the highest incidence occurring among patients with a history of seizure plus a history of anticonvulsant use. History of seizure but no history of anticonvulsant use, dementia, history of loss of consciousness, transient ischemic attack or cerebrovascular accident, and treated brain metastases were also associated with increased incidences of seizure [Bonafede, 2013].

CNS: Central Nervous System; mCRPC: Metastatic Castration-Resistant Prostate Cancer

Preventability:

A careful clinical evaluation and medical history can suggest a potentially increased risk for seizure. The decision to continue treatment in patients who develop seizure should be taken case by case.

Impact on the risk-benefit balance of the product:

Seizure is a rare event in enzalutamide-treated patients. The majority of seizure events observed in treated patients were single events that resolved after drug discontinuation and routine medical management. The impact on the risk-benefit balance of the product is considered low.

Public health impact:

Given the low incidence of seizure among enzalutamide-treated patients, the public health impact is considered to be limited.

Important Identified Risk: Fall

Potential mechanisms:

There is no known potential mechanism by which enzalutamide is associated with fall.

In general, several factors such as advanced age, generalized weakness, fatigue, dizziness, lower extremity weakness due to underlying advanced disease, and/or androgen deprivation, metastatic disease of the spinal column, or concomitant medication use may be associated with an increased risk of fall.

Evidence sources and strength of evidence:

This important identified risk is based on data from clinical studies. Fall is a very common adverse reaction that has been reported in patients treated with enzalutamide. In study MDV3100-13 (EMBARK), the incidence of fall was 21% in the enzalutamide + ADT group, 14.4% in placebo + ADT group and 15.8% in the enzalutamide monotherapy group. In study 9785-CL-0335 (ARCHES) in mHSPC patients, the incidence of fall was 6.5% versus 3.3% in the enzalutamide and placebo groups. In the pooled phase 3 studies, the incidence of fall was 11.5% versus 5.1% in the enzalutamide and placebo groups respectively. In MDV3100-14 (PROSPER), the incidence of fall was 17.6% versus 5.4% in the enzalutamide and placebo groups for the double-blind portion of the study. From the pooled phase 3 studies and phase 2 studies, the incidence of fall among the enzalutamide treated patients in the double-blind plus open label group was 12.7%. When adjusted for the duration of the exposure, the event rates of fall remained higher in the enzalutamide-treated groups compared with the placebo groups.

Characterization of the risk:

Frequencies and time-adjusted event rates for TEAEs of fall, as defined by the Fall PT, are summarized in [Table SVII.2] for MDV3100-13 (EMBARK), phase 3 studies, and total enzalutamide, by seriousness, action taken with study drug, severity, and timing of the event.

Review of postmarketing data for this important identified risk of Fall was consistent with findings in the clinical trial database. No new safety information pertaining to this risk emerged from postmarketing experience.

Table SVII.2 Treatment-emergent Adverse Events of Fall as Defined by the Preferred Term of Fall

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Fall – Overall	74 (21.0%)	51(14.4%)	56(15.8%)	428(11.5%)	145(5.1%)	649(12.7%)
Within the first 30 days	0/353	0/354	2/354 (0.6%)	13/3728 (0.3%)	12/2829 (0.4%)	24/5110 (0.5%)
Between 31 to 180 days	17/353 (4.8%)	5/353 (1.4%)	4/354 (1.1%)	100/3720 (2.7%)	40/2816 (1.4%)	134/5098 (2.6%)
Between 181 to 365 days	11/ 336(3.3%)	7/ 344(2.0%)	11/ 345(3.2%)	107/3200(3.3%)	28/1796(1.6%)	152/4389(3.5%)
Between 366 to 540 days	9/ 285(3.2%)	5/ 306(1.6%)	2/ 313(0.6%)	96/2554(3.8%)	20/1183(1.7%)	113/3530(3.2%)
Between 541 to 730 days	4/ 285(1.4%)	7/ 293(2.4%)	4/ 305(1.3%)	69/2027(3.4%)	16/ 735(2.2%)	97/2880(3.4%)
Between 731 to 900 days (2.5 years)	5/ 280(1.8%)	4/ 272(1.5%)	7/ 293(2.4%)	54/1521 (3.6%)	5/425 (1.2%)	80/2414(3.3%)
Between 2.5 to 3 Years	4/ 270(1.5%)	5/ 255(2.0%)	13/ 285(4.6%)	26/1116(2.3%)	8/ 333(2.4%)	69/2081(3.3%)
Between 3 to 4 Years	18/ 260(6.9%)	11/ 238(4.6%)	11/ 268(4.1%)	34/ 785(4.3%)	13/ 265(4.9%)	76/1790(4.2%)
Between 4 to 5 Years	14/ 244(5.7%)	17/ 205(8.3%)	11/ 238(4.6%)	15/ 504(3.0%)	17/ 207(8.2%)	49/1247(3.9%)
Between 5 to 6 Years	7/ 185(3.8%)	8/ 145(5.5%)	8/ 179(4.5%)	7/ 272(2.6%)	8/ 145(5.5%)	21/ 737(2.8%)
>6 Years	5/ 84(6.0%)	1/ 63(1.6%)	4/ 81(4.9%)	5/ 99(5.1%)	1/ 63(1.6%)	11/ 328(3.4%)
Fall Leading to Study Drug Discontinuation[3,4]	1 (0.3%)	0	2 (0.6%)	3 (0.1%)	1 (0.0%)	12(0.2%)
Fall Leading to Dose Interruption[4]	2 (0.6%)	3 (0.8%)	1 (0.3%)	11 (0.3%)	4 (0.1%)	17 (0.3%)
Fall Leading to Dose Reduction[4]	1 (0.3%)	0	0	1 (0.0%)	0	2 (0.0%)
Fall Leading to Death	0	0	0	0	0	0
Serious Fall	3 (0.8%)	2 (0.6%)	5 (1.4%)	27 (0.7%)	11 (0.4%)	53 (1.0%)
Grade 3 or Higher Fall	4 (1.1%)	4 (1.1%)	7 (2.0%)	43 (1.2%)	17 (0.6%)	80 (1.6%)
Within the first 30 days	0/353	0/354	0/354	1/3728 (0.0%)	1/2829 (0.0%)	1/5110 (0.0%)
Between 31 to 180 days	0/353	0/353	0/354	6/3720 (0.2%)	3/2816 (0.1%)	12/5098 (0.2%)
Between 181 to 365 days	2/336 (0.6%)	1/344 (0.3%)	2/345 (0.6%)	12/3200 (0.4%)	5/1796 (0.3%)	18/4389 (0.4%)
Between 366 to 540 days	0/285	0/ 306	0/ 313	11/2554 (0.4%)	1/1183 (0.1%)	14/3530 (0.4%)
Between 541 to 730 days	0/285	0/ 293	0/ 305	4/2027(0.2%)	2/ 735(0.3%)	9/2880(0.3%)
Between 731 to 900 days (2.5 years)	1/ 280(0.4%)	0/ 272	0/ 293	9/1521(0.6%)	1/ 425(0.2%)	10/2414(0.4%)
Between 2.5 to 3 Years	0/ 270	1/ 255(0.4%)	2/ 285(0.7%)	1/1116(0.1%)	2/ 333(0.6%)	6/2081(0.3%)
Between 3 to 4 Years	1/ 260(0.4%)	0/ 238	1/ 268(0.4%)	4/ 785(0.5%)	0/ 265	9/1790(0.5%)
Between 4 to 5 Years	0/ 244	1/ 205(0.5%)	1/ 238(0.4%)	0/ 504	1/ 207(0.5%)	6/1247(0.5%)
Between 5 to 6 Years	0/ 185	1/145 (0.7%)	1/ 179(0.6%)	0/ 272	1/ 145(0.7%)	1/ 737(0.1%)

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
>6 Years	0/84	0/63	0/81	0/99	0/63	0/328
Drug-Related[5] Fall	16 (4.5%)	11 (3.1%)	20 (5.6%)	54 (1.4%)	18 (0.6%)	108 (2.1%)
Grade 3 or Higher Drug-Related[5] Fall	1 (0.3%)	1 (0.3%)	3 (0.8%)	6 (0.2%)	3 (0.1%)	21 (0.4%)
Drug-Related[5] Serious Fall	1 (0.3%)	0	2 (0.6%)	6 (0.2%)	2 (0.1%)	19 (0.4%)
Grade 3 or 4 Fall	4 (1.1%)	4 (1.1%)	7 (2.0%)	43(1.2%)	17(0.6%)	80 (1.6%)
Within the first 30 days	0/353	0/354	0/ 354	1/3728 (0.0%)	1/2829 (0.0%)	1/5110 (0.0%)
Between 31 to 180 days	0/353	0/353	0/ 354	6/3720 (0.2%)	3/2816 (0.1%)	12/5098 (0.2%)
Between 181 to 365 days	2/336 (0.6%)	1/344 (0.3%)	2/345 (0.6%)	12/3200 (0.4%)	5/1796 (0.3%)	18/4389 (0.4%)
Between 366 to 540 days	0/285	0/306	0/313	11/2554 (0.4%)	1/1183 (0.1%)	14/3530 (0.4%)
Between 541 to 730 days	0/ 285	0/293	0/ 305	4/2027(0.2%)	2/ 735(0.3%)	9/2880(0.3%)
Between 731 to 900 days	1/ 280 (0.4%)	0/ 272	0/ 293	9/1521(0.6%)	1/ 425(0.2%)	10/2414(0.4%)
Between 2.5 to 3 Years	0/ 270	1/ 255(0.4%)	2/ 285(0.7%)	1/1116(0.1%)	2/ 333(0.6%)	6/2081(0.3%)
Between 3 to 4 Years	1/ 260 (0.4%)	0/238	1/ 268(0.4%)	4/ 785(0.5%)	0/ 265	9/1790(0.5%)
Between 4 to 5 Years	0/244	1/ 205(0.5%)	1/ 238(0.4%)	0/ 504	1/ 207(0.5%)	6/1247(0.5%)
Between 5 to 6 Years	0/185	1/ 145 (0.7%)	1/ 179(0.6%)	0/ 272	1/ 145(0.7%)	1/ 737(0.1%)
>6 Years	0/84	0/63	0/ 81	0/ 99	0/ 63	0/ 328

[1]Phase 3 studies include MDV3100-13 (ENZA+ADT and PBO+ADT arms), DB phase for MDV3100-14, 9785-CL-0335, CRPC2, MDV3100-03, and 9785-CL-0232.

[2]Phase2/3 enzalutamide include all enzalutamide-treated subjects during DB and/or OL period of MDV3100-13 (ENZA+ADT and ENZA Mono arms), MDV3100-14, 9785-CL-0335, CRPC2, MDV3100-03, 9785-CL-0232, 9785-CL-0222, and MDV3100-09.

[3]Fall leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

[4]It could be related to any study drug (enzalutamide and/or leuprolide, placebo).

[5]Drug-Related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug.

Note: Number of patients (n) reporting at least one event of Fall and percentage of these patients (%) are shown. NCI-CTCAE v4.03.

ADT: Androgen Deprivation Therapy; DB: Double-blind; ENZA: Enzalutamide; nmCSPC: Nonmetastatic Castration-Sensitive Prostate Cancer; OL: Open-label; PBO: Placebo.

Note: Nonmetastatic castration sensitive prostate cancer (nmCSPC) has been captured as per the ISS table which is equivalent to the indication nonmetastatic hormone sensitive prostate cancer (nmHSPC), proposed in the EMBARK study.

Cut-off dates: MDV3100-13: 31JAN2023, MDV3100-14:15OCT2019, 9785-CL-0335: 28MAY2021, CRPC2: 20FEB2018, MDV3100-03: 21MAR2019, 9785-CL-0232: 04NOV2020, 9785-CL-0222: 17FEB2018, MDV3100-09: 30MAY2018.

Risk factors and risk groups:

Risk Factor/Group	Description
Patient age	In phase 3 studies, the incidence of fall increased with increasing patient age in all treatment groups.
Prior events	Events of fall were not associated with prior events of syncope, presyncope, loss of consciousness, dizziness, postural dizziness.

Preventability:

Older people should take part in regular strength and balance training and regular physical exercise to reduce the risk of a fall.

Additionally, a multifactorial risk assessment and implementation of preventative measures at home may reduce the risk of fall. These measures have been shown to reduce the risk of fall [Chang et al, 2004].

Impact on the risk-benefit balance of the product:

Given the potential complications associated with fall in the treated population, the impact on benefit-risk balance is considered moderate.

Public health impact:

Fear of falling and reduction of mobility are the main impact on individuals. Fractures and injuries are possible complications. Complications of fall (e.g., fractures, head injury) may result in a decreased quality of life, especially in this elderly population.

Important Identified Risk: Non-pathological fracture

Note: There is a lack of diagnostic information or histological evidence in the reported cases of fracture, and consequently an inability to categorize reported fractures as pathological versus non-pathological.

Potential mechanisms:

There is no known potential mechanism by which enzalutamide is associated with non-pathological fractures.

In the controlled clinical studies, enzalutamide was given in combination with ADT. Hypogonadism (with decreased levels of testosterone and estradiol) due to ADT is associated with decreased bone mineral density secondary to decreased osteoblastic bone formation, increased bone resorption, increased bone turnover, and skeletal sensitivity to parathyroid hormone. Osteoporosis is a risk factor for fractures. ADT also decreases lean muscle mass which can increase the risk of fall, which can result in fractures [Tuck & Francis, 2009].

Evidence sources and strength of evidence:

This important identified risk is based on data from clinical studies. Fracture is a very common adverse reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of fracture was 18.4% in the enzalutamide + ADT

group, 13.6% in placebo + ADT group and 11.0% in the enzalutamide monotherapy group. In 9785-CL-0335 (ARCHES) in mHSPC patients and in the pooled phase 3 studies, the incidence of fracture was 9.6% versus 5.4% in Study 9785-CL-0335 (ARCHES) and 12.3% versus 5.8% in pooled phase 3 studies for enzalutamide and placebo group respectively. In MDV3100-14 (PROSPER), the incidence of fracture was 17.6% versus 6.0% for enzalutamide and placebo groups in the double-blind portion of the study. From the pooled phase 3 studies and phase 2 studies, the incidence of fracture among the enzalutamide treated patients in the double-blind plus open label group was 12.5%. When adjusted for the duration of the exposure, the event rates of fracture remained higher in the enzalutamide-treated groups compared with the placebo groups.

Characterization of the risk:

Frequencies and time-adjusted event rates for TEAEs of fracture (defined as all PTs under the MedDRA High Level Group Terms Fractures and Bone and joint injuries are summarized in [Table SVII.3] for MDV3100-13 (EMBARK), phase 3 studies, and total enzalutamide.

Note that fractures summarized in [Table SVII.3] include non-pathological and pathological/osteoporotic fractures. The most commonly reported fractures reported among enzalutamide-treated patients in the integrated safety population included Rib fracture (3.9%), Spinal compression fracture (1.4%) and Humerus fracture (0.7%).

Review of postmarketing data for this important identified risk of Non-pathological fracture was consistent with findings in the clinical trial database. No new safety information pertaining to this risk emerged from postmarketing experience.

Table SVII.3 Treatment-emergent Adverse Events of Fracture as Defined by the High-Level Group Terms of Fractures, and Bone and Joint Injuries

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Fracture – Overall	65 (18.4%)	48 (13.6%)	39 (11.0%)	457 (12.3%)	163 (5.8%)	640 (12.5%)
Within the first 30 days	1/353 (0.3%)	1/354 (0.3%)	2/354 (0.6%)	17/3728 (0.5%)	10/2829 (0.4%)	22/5110 (0.4%)
Between 31 to 180 days	5/353 (1.4%)	2/353 (0.6%)	2/354 (0.6%)	87/3720 (2.3%)	53/2816 (1.9%)	109/5098 (2.1%)
Between 181 to 365 days	6/336 (1.8%)	7/344 (2.0%)	8/345 (2.3%)	108/3200 (3.4%)	31/1796 (1.7%)	140/4389 (3.2%)
Between 366 to 540 days	8/285 (2.8%)	8/306 (2.6%)	2/313 (0.6%)	102/2554 (4.0%)	27/1183 (2.3%)	123/3530 (3.5%)
Between 541 to 730 days	6/285 (2.1%)	3/293 (1.0%)	4/305 (1.3%)	85/2027 (4.2%)	16/735 (2.2%)	111/2880 (3.9%)
Between 731 to 900 days	6/280 (2.1%)	4/272 (1.5%)	5/293 (1.7%)	50/1521 (3.3%)	5/425 (1.2%)	67/2414 (2.8%)
Between 2.5 to 3 Years	5/270 (1.9%)	4/255 (1.6%)	3/285 (1.1%)	22/1116 (2.0%)	7/333 (2.1%)	61/2081 (2.9%)
Between 3 to 4 Years	20/260 (7.7%)	9/238 (3.8%)	13/268 (4.9%)	36/785 (4.6%)	9/265 (3.4%)	80/1790 (4.5%)
Between 4 to 5 Years	13/244 (5.3%)	4/205 (2.0%)	7/238 (2.9%)	16/504 (3.2%)	4/207 (1.9%)	38/1247 (3.0%)
Between 5 to 6 Years	5/185 (2.7%)	8/145 (5.5%)	3/179 (1.7%)	5/272 (1.8%)	8/145 (5.5%)	13/737 (1.8%)
>6 Years	5/84 (6.0%)	0/63	1/81 (1.2%)	5/99 (5.1%)	0/63	8/328 (2.4%)
Fracture Leading to Study Drug Discontinuation[3,4]	0	0	0	12 (0.3%)	9 (0.3%)	23 (0.5%)
Fracture Leading to Dose Interruption[4]	3 (0.8%)	0	0	20 (0.5%)	2 (0.1%)	28 (0.5%)
Fracture Leading to Dose Reduction[4]	0	0	0	0	0	0
Fracture Leading to Death	0	0	0	1 (0.0%)	0	2 (0.0%)
Serious Fracture	10 (2.8%)	8 (2.3%)	8 (2.3%)	127 (3.4%)	46 (1.6%)	192 (3.8%)
Grade 3 or Higher Fracture	14 (4.0%)	9 (2.5%)	7 (2.0%)	124 (3.3%)	50 (1.8%)	188 (3.7%)
Within the first 30 days	1/353 (0.3%)	0/354	1/354 (0.3%)	6/3728 (0.2%)	5/2829 (0.2%)	9/5110 (0.2%)
Between 31 to 180 days	1/353 (0.3%)	0/353	1/354 (0.3%)	17/3720 (0.5%)	16/2816 (0.6%)	25/5098 (0.5%)
Between 181 to 365 days	2/336 (0.6%)	1/344 (0.3%)	1/345 (0.3%)	32/3200 (1.0%)	7/1796 (0.4%)	41/4389 (0.9%)
Between 366 to 540 days	1/285 (0.4%)	2/306 (0.7%)	1/313 (0.3%)	24/2554 (0.9%)	9/1183 (0.8%)	31/3530 (0.9%)
Between 541 to 730 days	1/285 (0.4%)	0/293	0/305	18/2027 (0.9%)	5/735 (0.7%)	25/2880 (0.9%)
Between 731 to 900 days	0/280	0/272	0/293	15/1521(1.0%)	1/425 (0.2%)	17/2414 (0.7%)
Between 2.5 to 3 Years	1/270 (0.4%)	1/255 (0.4%)	1/285 (0.4%)	4/1116 (0.4%)	3/333 (0.9%)	14/2081 (0.7%)
Between 3 to 4 Years	3/260 (1.2%)	2/238 (0.8%)	1/268 (0.4%)	8/785 (1.0%)	2/265 (0.8%)	23/1790 (1.3%)

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Between 4 to 5 Years	1/244 (0.4%)	2/205 (1.0%)	2/238 (0.8%)	2/504 (0.4%)	2/207 (1.0%)	9/1247 (0.7%)
Between 5 to 6 Years	2/185 (1.1%)	1/145 (0.7%)	0/179	2/272 (0.7%)	1/145 (0.7%)	3/737 (0.4%)
>6 Years	1/84 (1.2%)	0/63	0/81	1/99 (1.0%)	0/63	2/328 (0.6%)
Drug-Related[5] Fracture	13 (3.7%)	2 (0.6%)	5 (1.4%)	37 (1.0%)	11 (0.4%)	56 (1.1%)
Grade 3 or Higher Drug-Related[5] Fracture	2 (0.6%)	0	2 (0.6%)	8 (0.2%)	3 (0.1%)	15 (0.3%)
Drug-Related[5] Serious Fracture	1 (0.3%)	0	2 (0.6%)	6 (0.2%)	3 (0.1%)	14 (0.3%)
Grade 3 or 4 Fracture	14 (4.0%)	9 (2.5%)	7 (2.0%)	123 (3.3%)	50 (1.8%)	186(3.6%)
Within the first 30 days	1/353(0.3%)	0/354	1/354 (0.3%)	6/3728 (0.2%)	5/2829 (0.2%)	9/5110(0.2%)
Between 31 to 180 days	1/353 (0.3%)	0/353	1/354 (0.3%)	17/3720 (0.5%)	16/2816 (0.6%)	25/5098(0.5%)
Between 181 to 365 days	2/336 (0.6%)	1/344 (0.3%)	1/345 (0.3%)	32/3200 (1.0%)	7/1796 (0.4%)	41/4389(0.9%)
Between 366 to 540 days	1/285 (0.4%)	2/306 (0.7%)	1/313 (0.3%)	24/2554 (0.9%)	9/1183 (0.8%)	30/3530(0.8%)
Between 541 to 730 days	1/285 (0.4%)	0/293	0/ 305	18/2027 (0.9%)	5/735 (0.7%)	25/2880(0.9%)
Between 731 to 900 days	0/280	0/272	0/293	14/1521 (0.9%)	1/425 (0.2%)	16/2414(0.7%)
Between 2.5 to 3 Years	1/270 (0.4%)	1/255 (0.4%)	1/285 (0.4%)	4/1116 (0.4%)	3/333 (0.9%)	14/2081(0.7%)
Between 3 to 4 Years	3/260 (1.2%)	2/238 (0.8%)	1/268 (0.4%)	8/785 (1.0%)	2/265 (0.8%)	23/1790(1.3%)
Between 4 to 5 Years	1/244 (0.4%)	2/205 (1.0%)	2/238 (0.8%)	2/504 (0.4%)	2/207 (1.0%)	9/1247(0.7%)
Between 5 to 6 Years	2/185 (1.1%)	1/145 (0.7%)	0/179	2/272 (0.7%)	1/145 (0.7%)	3/ 737(0.4%)
>6 Years	1/84 (1.2%)	0/63	0/81	1/99 (1.0%)	0/63	2/ 328(0.6%)

[1] Phase 3 studies include MDV3100-13 (ENZA+ADT and PBO+ADT arms), DB phase for MDV3100-14, 9785-CL-0335, CRPC2, MDV3100-03, and 9785-CL-0232.
[2] Phase2/3 enzalutamide include all enzalutamide-treated subjects during DB and/or OL period of MDV3100-13 (ENZA+ADT and ENZA Mono arms), MDV3100-14, 9785-CL-0335, CRPC2, MDV3100-03, 9785-CL-0232, 9785-CL-0222, and MDV3100-09.
[3] Fracture leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.
[4] It could be related to any study drug (enzalutamide and/or leuprolide, placebo).
[5] Drug-Related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug.
Note: Number of patients (n) reporting at least one event of Fracture and percentage of these patients (%) are shown.
ADT: Androgen Deprivation Therapy; DB: Double-blind; ENZA: Enzalutamide; nmCSPC: Nonmetastatic Castration-Sensitive Prostate Cancer; OL: Open-label; PBO: Placebo
Note: Nonmetastatic castration sensitive prostate cancer (nmCSPC) has been captured as per the ISS table which is equivalent to the indication nonmetastatic hormone sensitive prostate cancer (nmHSPC), proposed in the EMBARK study.
Cut-off dates: MDV3100-13: 31JAN2023, MDV3100-14:15OCT2019, 9785-CL-0335: 28MAY2021, CRPC2: 20FEB2018, MDV3100-03: 21MAR2019, 9785-CL-0232: 04NOV2020, 9785-CL-0222: 17FEB2018, MDV3100-09: 30MAY2018.

Risk factors and risk groups:

Risk Factor/Group	Description
Administration of ADT	The incidences of all fractures and hip fractures requiring hospitalization in males treated with LHRH agonists were 9.8 and 6.3/1000 patient-years higher than the general population [Thorstenson et al, 2012]. In a review of 50613 males in the SEER-Medicare linked database diagnosed with prostate cancer between 1992 and 1997 who had survived at least 5 years after diagnosis, the incidence of fracture (both pathological and non-pathological) was 19.4% in patients who had been treated with ADT (medical or surgical); whereas the rate was 12.6% in patients who had not received treatment [Shahinian et al, 2005].
Age	Age is an independent risk factor for fractures in males with osteoporosis. Decreased lean body mass attributed to ADT, and, in general in patients with cancer, non-oncologic factors such as smoking, excessive alcohol use, inadequate exercise, calcium and vitamin D deficiency, parental history of hip fracture, use of glucocorticoids, proton pump inhibitors and anticoagulants are associated with increased risk of fracture [Lipton et al, 2012]. In general, in enzalutamide clinical trials, an increased incidence of fracture was observed with increasing age, consistent with the increased incidence of fall. The higher risk of fracture associated with fall in the enzalutamide group may be related to longer exposure time on study, along with the bone effects of prolonged androgen deprivation.

ADT: Androgen Deprivation Therapy; LHRH: Luteinizing Hormone-Releasing Hormone; SEER: Surveillance Epidemiology and End Results

Preventability:

In prostate cancer patients treated with ADT, treatment with bisphosphonates and selective estrogen receptor modulators (SERMs) has been shown to prevent bone loss [Greenspan, 2008]. The SERM toremifene has been demonstrated to reduce the risk of fractures in prostate cancer patients treated with ADT [Smith et al, 2013], as has the monoclonal antibody denosumab, which binds to Receptor Activator of Nuclear Factor-Kb-Ligand (RANKL), a receptor on the surface of osteoclasts which mediates bone resorption [Smith et al, 2009]. As possible, awareness of, and risk reduction for fall should help prevent non-pathological fractures.

Impact on the risk-benefit balance of the product:

Fractures in patients with prostate cancer may have significant morbidities, such as requiring hospitalization, as described above [Thorstenson et al, 2012]. Fractures associated with ADT are associated with increased mortality. Most fracture events reported in

enzalutamide-treated patients were grade 1 and grade 2 in severity and were rarely reported as serious events or events leading to enzalutamide discontinuation. Given the potential complications associated with non-pathological fracture in the treated population, the impact on benefit-risk balance is considered moderate.

Public health impact:

In the analyses of the SEER-Medicare linked database of 50 613 males with prostate cancer, the number needed to harm (NNH) for the occurrence of any fracture 12 to 60 months after diagnosis was 28 (95% CI: 26, 31) for any use of LHRH agonist and 16 (95% CI: 13, 19) for orchiectomy. Given an annual incidence of prostate cancer of > 220 000 in the US, given that more than 40% of patients receive LHRH agonists as an initial treatment and given a NNH of 28, approximately 3000 excess fractures per year would be attributable to the use of treatment with LHRH agonists [Shahinian et al, 2005]. The limited increase in non-pathological bone fractures that may be associated with enzalutamide therapy is expected to have limited potential impact on public health.

Important Identified Risk: Ischemic Heart Disease

Potential mechanisms:

There is no known potential mechanism by which enzalutamide is associated with ischemic heart disease, defined by 2 SMQs (Myocardial infarction SMQ and Other ischaemic heart disease SMQ [both narrow]).

Evidence sources and strength of evidence:

This important identified risk is based on data from clinical studies. Ischemic heart disease (including the following events observed in at least 2 patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarction, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischemia, and arteriosclerosis coronary artery) is a common adverse drug reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of Ischemic Heart disease (IHD) was higher in the enzalutamide monotherapy group (9%), as compared 5.4% in the enzalutamide + ADT group and 5.6% in placebo + ADT. In 9785-CL-0335 (ARCHES) in mHSPC patients the incidence of ischaemic heart disease was 2.8 % in the enzalutamide group, and in 1.9% in the placebo group. In MDV3100-14 (PROSPER), the incidence of ischemic heart disease was 6.5% versus 1.7% in enzalutamide and placebo groups in the double-blind portion of the study. In the phase 3 studies, the incidence of any event of ischemic heart disease was 3.5% in the enzalutamide group compared with 2.0% in the placebo group. From the pooled phase 3 studies and phase 2 studies, the incidence of ischemic heart disease among the enzalutamide treated patients in the double-blind plus open label group was 4.6%.When adjusted for duration of the exposure, the event rates of ischemic heart disease remained higher in the enzalutamide-treated group in the phase 3 studies compared with the placebo group.

Characterization of the risk:

Frequencies and time-adjusted event rates of treatment-emergent ischemic heart disease events, as defined by 2 SMQs (Myocardial infarction SMQ and Other ischaemic heart disease SMQ [both narrow]), are summarized in [Table SVII.4] for MDV3100-13 (EMBARK), phase 3 studies, and total enzalutamide, by system organ class (SOC), PT,

seriousness, action taken with study drug, severity, and timing of the event. No new safety information pertaining to this risk emerged from postmarketing experience.

Table SVII.4 Treatment-emergent Ischemic Heart Disease (IHD) Events as Defined by Narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Ischaemic Heart Disease (IHD) - Overall	19 (5.4%)	20 (5.6%)	32 (9.0%)	129 (3.5%)	57 (2.0%)	233 (4.6%)
Within the first 30 days	0/353	0/354	1/354 (0.3%)	2/3728 (0.1%)	6/2829 (0.2%)	4/5110 (0.1%)
Between 31 to 180 days	1/353 (0.3%)	3/353 (0.8%)	0/354	33/3720 (0.9%)	17/2816 (0.6%)	40/5098 (0.8%)
Between 181 to 365 days	2/336 (0.6%)	4/344 (1.2%)	6/345 (1.7%)	29/3200 (0.9%)	10/1796 (0.6%)	45/4389 (1.0%)
Between 366 to 540 days	1/285 (0.4%)	3/306 (1.0%)	2/313 (0.6%)	16/2554 (0.6%)	12/1183 (1.0%)	28/3530 (0.8%)
Between 541 to 730 days	2/285 (0.7%)	1/293 (0.3%)	3/305 (1.0%)	20/2027 (1.0%)	3/735 (0.4%)	34/2880 (1.2%)
Between 731 to 900 days	2/280 (0.7%)	2/272 (0.7%)	6/293 (2.0%)	14/1521 (0.9%)	2/425 (0.5%)	30/2414 (1.2%)
Between 2.5 to 3 Years	2/270 (0.7%)	4/255 (1.6%)	4/285 (1.4%)	11/1116 (1.0%)	5/333 (1.5%)	23/2081 (1.1%)
Between 3 to 4 Years	4/260 (1.5%)	2/238 (0.8%)	9/268 (3.4%)	7/785 (0.9%)	2/265 (0.8%)	33/1790 (1.8%)
Between 4 to 5 Years	4/244 (1.6%)	2/205 (1.0%)	2/238 (0.8%)	6/504 (1.2%)	2/207 (1.0%)	12/1247 (1.0%)
Between 5 to 6 Years	1/185 (0.5%)	2/145 (1.4%)	2/179 (1.1%)	1/272 (0.4%)	2/145 (1.4%)	8/737 (1.1%)
>6 Years	3/84 (3.6%)	0/63	1/81 (1.2%)	3/99 (3.0%)	0/63	7/328 (2.1%)
IHD Leading to Study Drug Discontinuation[4]	2 (0.6%)	4 (1.1%)	4 (1.1%)	10 (0.3%)	7 (0.2%)	23 (0.5%)
IHD Leading to Dose Interruption	2 (0.6%)	4 (1.1%)	5 (1.4%)	22 (0.6%)	12 (0.4%)	40 (0.8%)
IHD Leading to Dose Reduction	1 (0.3%)	0	1 (0.3%)	1 (0.0%)	1 (0.0%)	3 (0.1%)
IHD Leading to Death	0	1 (0.3%)	1 (0.3%)	14 (0.4%)	3 (0.1%)	23 (0.5%)
Serious IHD	13 (3.7%)	11 (3.1%)	23 (6.5%)	81 (2.2%)	32 (1.1%)	158 (3.1%)
Grade 3 or Higher IHD	14 (4.0%)	11 (3.1%)	21 (5.9%)	75 (2.0%)	33 (1.2%)	149 (2.9%)
Within the first 30 days	0/353	0/354	0/354	1/3728 (0.0%)	3/2829 (0.1%)	1/5110 (0.0%)
Between 31 to 180 days	1/353 (0.3%)	2/353 (0.6%)	0/354	8/3720 (0.2%)	9/2816 (0.3%)	13/5098 (0.3%)
Between 181 to 365 days	1/336 (0.3%)	1/344 (0.3%)	5/345 (1.4%)	15/3200 (0.5%)	4/1796 (0.2%)	29/4389 (0.7%)
Between 366 to 540 days	0/285	1/306 (0.3%)	2/313 (0.6%)	12/2554 (0.5%)	7/1183 (0.6%)	20/3530 (0.6%)
Between 541 to 730 days	2/285 (0.7%)	1/293 (0.3%)	2/305 (0.7%)	13/2027 (0.6%)	3/735 (0.4%)	21/2880 (0.7%)
Between 731 to 900 days	1/280 (0.4%)	2/272 (0.7%)	3/293 (1.0%)	11/1521 (0.7%)	2/ 425 (0.5%)	21/2414(0.9%)

	nmCSPC	nmCSPC	nmCSPC	Phase 3 Studies[1]		Total[2]
	MDV3100-13 ENZA+ADT (N = 353)	MDV3100-13 PBO+ADT (N = 354)	MDV3100-13 ENZA Mono (N = 354)	ENZA + ADT in DB (N = 3728) n/N (%)	PBO + ADT in DB (N = 2829) n/N (%)	Phase 2/3 ENZA+/-ADT in DB or OL (N = 5110) n/N (%)
Between 2.5 to 3 Years	0/270	2/255(0.8%)	2/285 (0.7%)	6/1116 (0.5%)	3/333 (0.9%)	13/2081 (0.6%)
Between 3 to 4 Years	4/260(1.5%)	1/238(0.4%)	5/268 (1.9%)	7/785 (0.9%)	1/265 (0.4%)	24/1790 (1.3%)
Between 4 to 5 Years	3/244(1.2%)	0/205	1/238 (0.4%)	4/504 (0.8%)	0/207	7/1247 (0.6%)
Between 5 to 6 Years	1/185(0.5%)	1/145(0.7%)	2/179 (1.1%)	1/272 (0.4%)	1/145 (0.7%)	6/737 (0.8%)
>6 Years	3/84(3.6%)	0/63	1/81 (1.2%)	3/99 (3.0%)	0/63	5/328 (1.5%)
Drug-Related[5] IHD	5 (1.4%)	6 (1.7%)	8 (2.3%)	18 (0.5%)	14 (0.5%)	40 (0.8%)
Grade 3 or Higher Drug-Related[5] IHD	3 (0.8%)	3 (0.8%)	5 (1.4%)	10 (0.3%)	9 (0.3%)	24 (0.5%)
Drug-Related[5] Serious IHD	3 (0.8%)	3 (0.8%)	4 (1.1%)	11 (0.3%)	8 (0.3%)	23 (0.5%)
Grade 3 or 4 IHD	14 (4.0%)	11 (3.1%)	20 (5.6%)	62 (1.7%)	31 (1.1%)	128 (2.5%)
Within the first 30 days	0/353	0/354	0/354	0/3728	3/2829 (0.1%)	0/5110
Between 31 to 180 days	1/353 (0.3%)	2/353 (0.6%)	0/354	6/3720 (0.2%)	7/2816 (0.2%)	11/5098 (0.2%)
Between 181 to 365 days	1/336 (0.3%)	1/344 (0.3%)	5/345 (1.4%)	12/3200 (0.4%)	4/1796 (0.2%)	23/4389 (0.5%)
Between 366 to 540 days	0/285	1/306 (0.3%)	2/313 (0.6%)	9/2554 (0.4%)	7/1183 (0.6%)	17/3530 (0.5%)
Between 541 to 730 days	2/285 (0.7%)	1/293 (0.3%)	2/305 (0.7%)	11/2027 (0.5%)	3/735 (0.4%)	19/2880 (0.7%)
Between 731 to 900 days	1/280 (0.4%)	2/272 (0.7%)	3/293 (1.0%)	10/1521 (0.7%)	2/425 (0.5%)	18/2414 (0.7%)
Between 2.5 to 3 Years	0/270	2/255 (0.8%)	2/285 (0.7%)	5/1116 (0.4%)	3/ 333(0.9%)	12/2081 (0.6%)
Between 3 to 4 Years	4/260 (1.5%)	1/238 (0.4%)	4/268 (1.5%)	7/785 (0.9%)	1/265 (0.4%)	20/1790 (1.1%)
Between 4 to 5 Years	3/244 (1.2%)	0/205	1/238 (0.4%)	4/504 (0.8%)	0/207	7/1247 (0.6%)
Between 5 to 6 Years	1/185 (0.5%)	1/145 (0.7%)	2/179 (1.1%)	1/272 (0.4%)	1/145 (0.7%)	6/737 (0.8%)
>6 Years	3/84 (3.6%)	0/63	1/81 (1.2%)	3/99 (3.0%)	0/63	5/328 (1.5%)

[1]Phase 3 studies include MDV3100-14 (PROSPER), 9785-CL-0335, CRPC2, MDV3100-03, and 9785-CL-0232.

[2]Total enzalutamide includes subjects who were treated with enzalutamide during DB phase of 9785-CL-0335 and 9785-CL-0232 or the DB and/or OL phases of MDV3100-14 (PROSPER), CRPC2, MDV3100-03, 9785-CL-0222, and MDV3100-09.

[3]Ischaemic Heart Disease identified as primary reason for study drug discontinuation is from treatment discontinuation CRF.

[4]Ischaemic Heart Disease leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

[5]Related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug.

Note: Number of patients (n) reporting at least one event of Ischaemic Heart Disease and percentage of these patients (%) are shown. NCI-CTCAE v4.03.

ADT: Androgen Deprivation Therapy; DB: Double-blind; ENZA: Enzalutamide; nmCSPC: Nonmetastatic Castration-Sensitive Prostate Cancer; OL: Open-label; PBO: Placebo.

Note: Nonmetastatic castration sensitive prostate cancer (nmCSPC) has been captured as per the ISS table which is equivalent to the indication nonmetastatic hormone sensitive prostate cancer (nmHSPC), proposed in the EMBARK study.

Cut-off dates: MDV3100-14: 15OCT2019, 9785-CL-0335: 28MAY2021, CRPC2: 20FEB2018, MDV3100-03: 21MAR2019, 9785-CL-0232: 04NOV2020, 9785-CL-0222: 17FEB2018, MDV3100-09: 30MAY2018

A univariate logistic regression analysis of patients with ischemic heart disease (narrow SMQs “Myocardial infarction” and “Other ischemic heart disease”), yes/no, conducted without integration of Study 9785-CL-0335 (ARCHES) and MDV3100-13 (EMBARK), showed that many factors were potentially associated with ischemic heart disease in both MDV3100-14 (PROSPER) and the 3 pooled phase 3 studies (MDV3100-14, MDV3100-03 [PREVAIL], and CRPC2 [AFFIRM]). These factors included treatment, age, history of hypertension (MDV3100-14 only), history of cardiovascular disease, history of myocardial infarction, history of cardiac failure and history of dyslipidemia [RMP v12.5 Ad hoc Table 12.5]. In the stepwise multivariate logistic regression analysis, the strongest factors were history of cardiovascular disease and treatment for both MDV3100-14 and the pooled phase 3 studies MDV3100-14, MDV3100-03, and CRPC2 [RMP v12.5 Ad hoc Table 12.6]. Age was also statistically significant in the pooled phase 3 studies MDV3100-14, MDV3100-03, and CRPC2.

However, the logistic regression analyses do not take the imbalance in treatment-emergent follow-up times between the treatment groups into consideration. The stepwise multivariate Cox regression models of time to first ischemic heart disease event did not find treatment group to be significantly associated with time to first ischemic heart disease event (P-values > 0.20 for any grade, grade 3 or 4 events, or grade ≥ 3 events) ([Table SVII.4] and [RMP v12.5 Ad hoc Tables 12.8.1 and 12.9.1]). The factor most associated with time to first ischemic heart disease event was history of cardiovascular disease in MDV3100-14 and the pooled phase 3 studies MDV3100-14, MDV3100-03, and CRPC2. History of myocardial infarction was also significant in MDV3100-14.

Evidence from multiple large observational studies suggests that men treated with ADT are at increased risk of cardiovascular events [Bosco et al, 2015; Zhao et al, 2014]. Throughout the enzalutamide development program, rates of safety endpoints have been determined among men randomized to enzalutamide and ADT or placebo and ADT. As such, it is important to understand the contribution of background ADT therapy, as men treated with enzalutamide also continue on ADT. In the monotherapy arm of EMBARK, increased levels of testosterone and presumably estrogen may have contributed to risk.

While the percentage of patients with ischemic heart disease events was higher in the enzalutamide groups of the pooled phase 3 studies (MDV3100-14, MDV3100-03, CRPC2, 9785-CL-0232, 9785 CL-0335 and MDV3100-13), the duration of treatment was also longer compared with the placebo groups resulting in a longer treatment-emergent period. When ischemic heart disease events were adjusted for the length of the treatment-emergent period, using event rate per 100 patient-years, the findings suggest that the incidence rates were still numerically higher on enzalutamide; however, the differences between enzalutamide and placebo in the pooled phase 3 studies were 2.2 vs 1.9 for cardiac disorder events. After adjusting for time, event rates for Myocardial Infarction SMQ on enzalutamide plus ADT is similar to ADT alone. Of note, 1 patient on the enzalutamide-treated arm in PROSPER had 9 ischemic heart disease events, which may have contributed to the numerical imbalance.

Additional stepwise multivariate analyses, using logistic regression and Cox proportional hazards models, were conducted to explore a potential association of enzalutamide treatment with ischemic heart disease, while controlling for statistically significant baseline cardiovascular risk factors associated with ischemic heart disease (excluding Study 9785-CL-0335 [ARCHES]). The logistic regression models did find that factors, particularly history of cardiovascular disease and treatment were significantly associated with patients experiencing an ischemic heart disease event.

However, these analyses do not consider the difference for the lengths of the treatment-emergent periods between the enzalutamide and placebo groups. The Cox proportional hazards regression models, using time to event, better account for this difference. These models found history of cardiovascular disease to be the main factor associated with ischemic heart disease events in the 3 pooled phase 3 studies (MDV3100-14, MDV3100-03, and CRPC2) and MDV3100-14 alone. History of myocardial infarction was also a significant factor in MDV3100-14. Treatment was not significantly associated with time to first ischemic heart disease event in either the pooled phase 3 studies (MDV3100-14, MDV3100-03, and CRPC2) or MDV3100-14 alone, P-value > 0.20.

In summary, although several risk factors for ischemic heart disease exist in this population including treatment with ADT, there is a reasonable possibility that enzalutamide is associated with ischemic heart disease events, based on the higher frequency of events observed in enzalutamide patients as compared to the placebo group.

Risk factors and risk groups:

Risk Factor/Group	Description
History of cardiovascular disease	Adverse cardiac events are a recognized risk with ADT.
History of dyslipidemia	Adverse cardiac events are a recognized risk with ADT.
Age ≥ 75 years	Adverse cardiac events are a recognized risk with ADT.

ADT: Androgen deprivation therapy

Preventability:

Ischemic heart disease can be partially prevented by control of the patient's hypertension, diabetes, and lipids, as well as maintaining a healthy weight and diet, regular exercise, limiting alcohol use, and not smoking.

Impact on the risk-benefit balance of the product:

Ischemic heart disease can be potentially life-threatening or have a fatal outcome. The CRPC patient population can range from asymptomatic, nmCRPC patients without cardiovascular history and with a rather high quality of life at baseline, as measured by Time to Degradation of the Functional Assessment of Cancer Therapy-Prostate (FACT-P), Global Score, European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate (25QLQ-PR25), to elderly men with advanced disease and/or pre-existing cardiovascular

history. Therefore, the risk of ischemic heart disease may have an impact on the risk-benefit balance for patients depending on their stage of disease and if they have pre-existing cardiovascular risk factors.

Public health impact:

In clinical trials, the overall frequency of ischemic heart disease events in enzalutamide-treated patients in the integrated safety population was 4.6%. Given the potential severity of ischemic heart disease, appropriate monitoring and control of underlying cardiovascular disease can mitigate the impact on public health.

Important Potential Risk: Not applicable

There are no important potential risks for enzalutamide.

SVII.3.2 Presentation of the missing information

There is no missing information for enzalutamide.

PART II: MODULE SVIII. SUMMARY OF THE SAFETY CONCERNS

Data-lock point for this Module	30 Aug 2018
Version when Module last updated	12.5

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Seizure • Fall • Non-pathological fracture • Ischaemic Heart Disease
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

III.1 Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

Specific adverse reaction follow-up questionnaires

Description	Purpose	Safety concern(s) addressed
Fall TDQ for spontaneous reports	• Monitoring, standardized collection, and documentation of AE reports of fall to determine whether additional measures for prevention are needed. • To gain further knowledge into the nature of reported AEs of fall in order to determine any preceding events and risk factors.	• Fall
Fracture TDQ for spontaneous reports	• Monitoring, standardized collection, and documentation of AE reports of fracture to determine whether additional measures for prevention are needed. • To gain further knowledge into the nature of reported AEs of fracture in order to determine any preceding events and risk factors.	• Non-pathological fracture

AE: Adverse Event; TDQ: Targeted Data Questionnaire.

Adverse event follow-up questionnaires are provided in [Annex 4]

Other forms of routine pharmacovigilance activities

Activity	Objective(s)/Description	Milestone(s)
Safety analysis of event of fall in CSRs of individual enzalutamide clinical trials	Detailed analysis of fall (designated as event of Interest) as part of CSRs of individual studies, in order to gain further knowledge into the nature of the important identified risk of Fall	Completion of CSRs for individual studies including EMBARK
Safety analysis of event of fracture in CSRs of individual enzalutamide clinical trials	Detailed analysis of fracture (designated as event of Interest) as part of CSRs of individual studies, in order to gain further knowledge into the nature of the important identified risk of Non-pathological fracture	Completion of CSRs for individual studies including EMBARK
Safety analyses of events of ischemic heart disease in CSRs of individual enzalutamide clinical trials	Detailed analyses of ischemic heart disease events (risk factors, patient's demographics, relevant medical history) as part of CSRs of individual studies, in order to gain further knowledge into the nature, frequency, severity, seriousness, and outcome of the important identified risk of Ischemic heart disease, as well as into causal association with enzalutamide.	Completion of CSRs for individual studies including EMBARK

CSR: Clinical Study Report.

III.2 Additional pharmacovigilance activities

None; there are no additional pharmacovigilance activities.

Study short name and title	None
Rationale and study objectives	Not applicable
Study design	Not applicable
Study population	Not applicable
Milestones	Not applicable

III.3 Summary table of additional pharmacovigilance activities

Not applicable; there are no additional pharmacovigilance activities.

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
Not Applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit risk)				
Not Applicable				

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
Not Applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Data-lock point for this Module	15 Oct 2019
Version when Module last updated	15.0

There are no planned or ongoing postauthorization efficacy studies.

Table Part IV.1: Planned and ongoing postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorization				
None	Not applicable	Not applicable	Not applicable	Not applicable
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Seizure	Routine risk communication: • SmPC sections 4.4, 4.7, 4.8, and 4.9; • PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • 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.
Fall	Routine risk communication: • SmPC Section 4.8; • PL Section 4.
Non-pathological fracture	Routine risk communication: • SmPC Section 4.8; • PL Section 4.
Ischemic heart disease	Routine risk communication: • SmPC Section 4.8; • PL Section 4.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. There are no additional risk minimization measures.

V.2.1 Removal of additional risk minimization activities

Activity	Safety concerns addressed	Rationale for the removal of additional risk minimization activity
Not applicable		

V.3 Summary of Risk Minimization Measures

Table Part V.3: 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 TDQ for spontaneous reports; • 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: • Fracture TDQ for spontaneous reports; • 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.

CSR: Clinical Study Report; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TDQ: Targeted Data Questionnaire.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Data-lock point for this Module	31 Jan 2023
Version when Module last updated	18.0

Summary of risk management plan for XTANDI (Enzalutamide)

This is a summary of the RMP for XTANDI®. The RMP details important risks of XTANDI, how these risks can be minimized, and how more information will be obtained about XTANDI's risks and uncertainties (missing information).

XTANDI's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how XTANDI should be used.

This summary of the RMP for XTANDI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of XTANDI's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

XTANDI is authorized for the treatment of adult men with high risk nmCRPC, the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated, and the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy (see the SmPC for the full indication). Xtandi is also authorized for expanded indication for the treatment of adult men with mHSPC. It is proposed that indication be expanded for the treatment of adult men with high-risk BCR nmHSPC who are unsuitable for salvage- radiotherapy. Thus, the overall target indication is the treatment of patients with mHSPC, nmHSPC, mCRPC and nmCRPC. It contains enzalutamide as the active substance, and it is given orally as tablets or capsules (four 40 mg oral capsules once daily or four 40 mg oral film-coated tablets once daily or two 80 mg oral film-coated tablets once daily).

Further information about the evaluation of XTANDI's benefits can be found in XTANDI's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002639/human_med_001663.jsp&mid=WC0b01ac058001d124

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of XTANDI, together with measures to minimize such risks and the proposed studies for learning more about XTANDI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of XTANDI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XTANDI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Seizure • Fall • Non-pathological fracture • Ischaemic Heart Disease
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Seizure	
Evidence for linking the risk to the medicine	This important identified risk is based on data from enzalutamide toxicology studies in animals and clinical studies. Seizures were observed in animals in nonclinical toxicology studies (1 rat and 2 dogs) administered enzalutamide, and there was a dose-dependent increase of seizures in mice. The event of seizure is an uncommon adverse drug reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of seizure was 1.1% in the enzalutamide + ADT group as compared to 0.8% in the enzalutamide monotherapy group. There was no incidence of

	seizure in placebo + ADT group. In 9785-CL-0335 (ARCHES) in mHSPC patients the incidence of the event of seizure was lower in the enzalutamide group compared with the placebo group (0.3% vs. 0.5%). In MDV3100-14 (PROSPER), the incidence of seizure was low in both groups, but numerically higher in the enzalutamide group compared with the placebo group (0.3% vs 0% in the double-blind portion of the study. In the phase 3 studies in patients with mHSPC and with nmCRPC and mCRPC, the incidence of any event of seizures was 0.4% in the enzalutamide group compared with 0.1% in the placebo group. From the pooled phase 3 studies and phase 2 studies, the incidence of seizures among the enzalutamide treated patients in the double-blind plus open label group was 0.6%. When adjusted for duration of exposure, the event rates of seizure remained higher in the enzalutamide-treated groups compared with the placebo groups for the phase 3 studies but not for Study 9785-CL-0335
Risk factors and risk groups	Dose appears to be an important predictor of the risk of seizure, as reflected by nonclinical data and clinical trial experience with enzalutamide at higher doses (a dose-response relationship between enzalutamide and seizure was suggested in a dose escalation study). In a single-arm postmarketing safety study to assess the risk of seizure in patients with predisposing factors for seizure (9785-CL- 0403), the seizure event rate among enzalutamide-treatment mCRPC patients who were potentially at an increased risk of seizure was 1.1%, which was comparable with the seizure rate in the other studies, despite the inclusion of patients with potential risk factors for seizure. The occurrence of seizure in patients diagnosed with prostate cancer has been reported in the literature mainly in association with central nervous system metastases, which are exceedingly rare in prostate cancer. In a retrospective cohort study, the incidence of seizure in mCRPC patients was higher in patients with at least 1 risk factor than in those with no risk factors, with the highest incidence occurring among patients with a history of seizure plus a history of anticonvulsant use. History of seizure but no history of anticonvulsant use, dementia, history of loss of consciousness, transient ischemic attack or cerebrovascular accident, and treated brain metastases were also associated with increased incidences of seizure [Bonafede, 2013].
Risk minimization measures	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.

ADT: Androgen Deprivation Therapy; CRPC: Castration-Resistant Prostate Cancer; HSPC: Hormone-Sensitive Prostate Cancer; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Important Identified Risk: Fall	
Evidence for linking the risk to the medicine	This important identified risk is based on data from clinical studies. Fall is a very common adverse reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of fall was 21% in the enzalutamide + ADT group, 14.4% in placebo + ADT group and 15.8% in the enzalutamide monotherapy group. In study 9785-CL- 0335 (ARCHES) in metastatic HSPC patients and in the pooled phase 3 studies, the incidence of fall was 6.5% versus 3.3% in Study 9785-CL-0335 (ARCHES) and 11.5% versus 5.1 % for enzalutamide and placebo group respectively. In MDV3100-14 (PROSPER), the incidence of fall was 17.6% versus 5.4% in the enzalutamide and placebo groups for the double-blind portion of the study. From the pooled phase 3 studies and phase 2 studies, the incidence of fall among the enzalutamide treated patients in the double-blind plus open label group was 12.7%. When adjusted for the duration of the exposure, the event rates of fall remained higher in the enzalutamide-treated groups compared with the placebo.
Risk factors and risk groups	In phase 3 studies, the incidence of fall increased with increasing patient age in all treatment groups. The events of fall among enzalutamide-treated patients did not appear to be associated with prior events of syncope, presyncope, loss of consciousness, dizziness, or postural dizziness.
Risk minimization measures	Routine risk communication: • SmPC Section 4.8; • PL Section 4. Additional risk minimization measures: • None

ADT: Androgen Deprivation Therapy; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Important Identified Risk: Non-pathological fracture	
Evidence for linking the risk to the medicine	This important identified risk is based on data from clinical studies. Fracture is a very common adverse reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of fracture was 18.4% in the enzalutamide + ADT group, 13.6% in placebo + ADT group and 11% in the enzalutamide monotherapy group. In 9785-CL-0335 (ARCHES) in mHSPC patients and in the pooled phase 3 studies, the incidence of fracture was 9.6% versus 5.4% in Study 9785-CL-0335 (ARCHES) and 12.3% versus 5.8% for enzalutamide and placebo group respectively. In MDV3100-14 (PROSPER),

	the incidence of fracture was 17.6% versus 6.0% for enzalutamide and placebo groups in the double-blind portion of the study. From the pooled phase 3 studies and phase 2 studies, the incidence of fracture among the enzalutamide treated patients in the double-blind plus open label group was 12.5%. When adjusted for the duration of the exposure, the event rates of fracture remained higher in the enzalutamide-treated groups compared with the placebo groups.
Risk factors and risk groups	In prostate cancer, ADT is a risk for fracture. The incidences of all fractures and hip fractures requiring hospitalization in males treated with LHRH agonists were 9.8 and 6.3/1000 PY higher than the general population [Thorstenson et al, 2012]. In a review of 50 613 males in the SEER-Medicare linked database diagnosed with prostate cancer between 1992 and 1997 who had survived at least 5 years after diagnosis, the incidence of fracture (both pathological and non-pathological) was 19.4% in patients who had been treated with ADT (medical or surgical); whereas the rate was 12.6% in patients who had not received treatment [Shahinian et al, 2005]. Age is an independent risk factor for fractures in males with osteoporosis. Decreased lean body mass attributed to ADT, and, in general in patients with cancer, non-oncologic factors such as smoking, excessive alcohol use, inadequate exercise, calcium and vitamin D deficiency, parental history of hip fracture, use of glucocorticoids, proton pump inhibitors and anticoagulants are associated with increased risk of fracture [Lipton et al, 2012]. In general, in enzalutamide clinical trials, an increased incidence of fracture was observed with increasing age, consistent with the increased incidence of fall. The higher risk of fracture associated with fall in the enzalutamide group may be related to longer exposure time on study along with the bone effects of prolonged androgen deprivation.
Risk minimization measures	Routine risk communication: • SmPC Section 4.8; • PL Section 4. Additional risk minimization measures: • None

ADT: Androgen Deprivation Therapy; LHRH: Luteinizing Hormone-Releasing Hormone; HSPC: Hormone-Sensitive Prostate Cancer; PL: Package Leaflet; PY: Patient-Years; SEER: Surveillance Epidemiology and End Results; SmPC: Summary of Product Characteristics.

Important Identified Risk: Ischemic Heart Disease	
Evidence for linking the risk to the medicine	This important identified risk is based on data from clinical studies. Ischemic heart disease (including the following events observed in at least 2 patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarction, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischemia, and arteriosclerosis coronary artery) is a common adverse drug reaction that has been reported in patients treated with

	enzalutamide. In MDV3100-13 (EMBARK), the incidence of IHD was higher in the enzalutamide monotherapy group (9%), as compared 5.4% in the enzalutamide + ADT group and 5.6% in placebo + ADT. In 9785-CL-0335 (ARCHES) in metastatic HSPC patients the incidence of ischaemic heart disease was 2.8% in the enzalutamide group, and in 1.9% in the placebo group. In PROSPER, the incidence of ischemic heart disease was 6.5% vs 1.7% in enzalutamide and placebo groups. In the phase 3 studies, the incidence of any event of ischemic heart disease was 3.5% in the enzalutamide group compared with 2.0% in the placebo group. From the pooled phase 3 studies and phase 2 studies, the incidence of ischaemic heart disease among the enzalutamide treated patients in the double-blind plus open label was 4.6%. When adjusted for duration of the exposure, the event rates of ischemic heart disease remained higher in the enzalutamide-treated group in the phase 3 studies compared with the placebo group.
Risk factors and risk groups	Risk factors for experiencing an ischemic event included a history of one or more of the following: cardiovascular disease, dyslipidemia, and age ≥ 75 years. Adverse cardiac events are a recognized risk with ADT.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8; • PL Section 4. Additional risk minimization measures: • None

ADT: Androgen Deprivation Therapy; HSPC: Hormone-Sensitive Prostate Cancer; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of XTANDI.

II.C.2 Other studies in postauthorization development plan

There are no studies required for XTANDI.

PART VII: ANNEXES

Table of Contents

Annex 1 - EudraVigilance Interface

Annex 1 is not in scope for publication

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

Annex 2 is not in scope for publication

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Annex 3 is not in scope for publication

Annex 4 - Specific adverse event follow-up forms

Data-lock point for this annex	31 Jan 2023
Version when annex last updated	18.0

Fall Follow-up Questionnaire

Email to:		**Case Number**	
Fax to:		**Patient Details:**	Age/Age group ☐ Male ☐ Female

Instructions

With this questionnaire, we would like to request specific follow-up information regarding the case you reported for a fall experienced during the use of <Astellas product>. Provide as much new information as possible, focusing on the information that has not previously been provided and that is relevant for the fall case. Consider the applicable data privacy restrictions in your country while completing this form. For cases not originating from clinical studies, attach any relevant anonymized supporting documentation, if available.

Thank you in advance for your cooperation.

Case Number:			
Reported Event:		**Patient Details:**	Age/Age group ☐ Male ☐ Female

Thank you for reporting the initial report related to Fall during the use of <Astellas product>.
With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case.

SIGNS AND SYMPTOMS OF THE EVENT	
☐ Bleeding/haematoma	☐ Shock
☐ Fracture:	☐ Sprain/Strain
☐ Head injury	☐ Swelling
☐ Other local/systemic injury:	☐ Other:
☐ Pain	

UNDERLYING CONDITIONS / RISK FACTORS	
☐ Alcohol use (units per week) preceding fall:	☐ Medical condition predisposing for fall:
☐ Cognitive impairment:	☐ Musculoskeletal pain
☐ Difficulty walking	☐ Narcotics use preceding fall
☐ Dizziness/vertigo	☐ Presyncope/ Syncope
☐ Fatigue	☐ Seizure
☐ History of other falls in the past year:	☐ Unsteady gait
☐ Known joints problems (joint pain, non-optimal functioning of certain joint, arthritis, knee/hip prosthesis):	☐ Possible drug interaction
	☐ Prostheses
☐ Limb/foot abnormality:	☐ Smoking (packs per week):

☐ Loss of consciousness	☐ Other:

MEDICATION

DRUG NAME	SUSPECT PRODUCT (S) CONCOMITANT (C) AE TREATMENT (T)	INDICATION	DOSE/FREQUENCY/ ROUTE OF ADMINISTRATION	START DATE dd-Mmm-yyyy	STOP DATE *dd-Mmm-yyyy* or *Ongoing*
☐					
☐					
☐					

RELEVANT INVESTIGATIONS *Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.*

INVESTIGATION	DATE dd-Mmm-yyyy	RESULT/UNIT
☐		
☐		
☐		
☐		
☐ Other:		

ADDITIONAL DETAILS / OTHER RELEVANT INFORMATION

Additional details, including duration of signs and symptoms and details of fall (i.e. stumbled, slipped, etc.):

REPORTER INFORMATION

REPORTER NAME / CREDENTIALS	DATE (dd-Mmm-yyyy)	SIGNATURE (to confirm the accuracy of the data)

Fracture Follow-up Questionnaire

Email to:		**Case Number**	
Fax to:		**Patient Details:**	Age/Age group ☐ Male ☐ Female

Instructions

With this questionnaire, we would like to request specific follow-up information regarding the case you reported for fracture experienced during the use of <Astellas product>. Provide as much new information as possible, focusing on the information that has not previously been provided and that is relevant to the fracture case. Consider the applicable data privacy restrictions in your country while completing this form. For cases not originating from clinical studies, attach any relevant anonymized supporting documentation, if available.

Thank you in advance for your cooperation.

Case Number:					
Reported Event:		**Patient Details:**	Age/Age group	☐ Male ☐ Female	
Thank you for reporting the initial report related to fracture during the use of <Astellas product>. *With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case.*					
SIGNS AND SYMPTOMS OF THE EVENT					
☐ Bleeding/haematoma		☐ Shock			
☐ Pain		☐ Other			
SPECIFY THE UNDERLYING CAUSE OF THE FRACTURE:		☐ Fall (specify underlying cause of the fall):			
☐ Incidental finding (during imaging, etc)		☐ Accident/trauma:			
☐ Fracture at site of bone metastases		☐ Other underlying cause:			
UNDERLYING CONDITIONS / RISK FACTORS					
☐ Alcohol use (units per week):		☐ Overweight			
☐ ADT therapy: ☐ Surgical castration ☐ LHRH agonist/antagonist		☐ Previous fracture(s)			
☐ Arteriosclerosis obliterans (or peripheral arterial disease)		☐ Prosthesis			
☐ Bone metastases		☐ Underweight			
☐ Diabetes		☐ Possible drug interaction			
☐ Osteopenia		☐ Smoking (packs per week):			
☐ Osteoporosis		☐ Other:			
MEDICATION					
DRUG NAME	**SUSPECT PRODUCT (S) CONCOMITANT (C) AE TREATMENT (T)**	**INDICATION**	**DOSE/FREQUENCY/ ROUTE OF ADMINISTRATION**	**START DATE** dd-Mmm-yyyy	**STOP DATE** *dd-Mmm-yyyy* or *Ongoing*

☐ Bisphosphonates					
☐ LHRH agonist/antagonist					
☐ Prednisolone therapy					
☐					

RELEVANT INVESTIGATIONS *Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.*

INVESTIGATION	**DATE** dd-Mmm-yyyy	**RESULT/UNIT**
☐ Bone Density		
☐ Imaging		
☐ Other:		

ADDITIONAL DETAILS / OTHER RELEVANT INFORMATION

Provide additional details about the fracture, including the type and location of the fracture (and any previous fractures).

REPORTER INFORMATION

REPORTER NAME / CREDENTIALS	**DATE** (dd-Mmm-yyyy)	**SIGNATURE** (to confirm the accuracy of the data)

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Annex 5 is not in scope for publication

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Data-lock point for this annex	30 Aug 2018
Version when annex last updated	12.1

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Annex 7 is not in scope for publication

Annex 8 - Summary of changes to the risk management plan over time

Annex 8 is not in scope for publication

Signature is kept of file