EU RISK MANAGEMENT PLAN (RMP)

NUBEQA®

BAY 1841788
(Darolutamide)

No.5.1

Date of Report:
25 SEP 2024

[redacted]

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EU Risk Management Plan

EU Risk Management Plan for Nubeqa (Darolutamide)

RMP version to be assessed as part of this application:

RMP Version number: 5.1

Data lock point for this RMP: 07 JUN 2024

Date of final sign-off: 25 SEP 2024

Rationale for submitting an updated Risk management Plan (RMP):

The RMP Version 5.1 is submitted with the type II variation procedure which proposes the extension of indication for darolutamide: Nubeqa is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.

Summary of significant changes in this RMP from Version 4.1:

- Part I – Section updated in-line with the proposed Summary of Product Characteristics (SmPC). Change in the table product overview: No additional monitoring in the European Union (EU), following the five-year renewal outcome.
- Part II SI – This module was updated with the more recent epidemiology data.
- Part II SIII – Update of the exposure data for the clinical development programme.
- Part II SV – Post-marketing exposure data was updated.
- Part II SVII – This module was updated to include clinical trial data from Phase 3 ARANOTE [21140] study and post-marketing data. Correction made to reflect the information in the EU SmPC for the recommended dose in patients with moderate and severe hepatic impairment.
- Part VI – Summary was updated to reflect the changes introduced to the respective modules of this RMP.
- Part VII – Annex 7.1: Literature references were updated. Annex 8: Updates to the summary of changes to the RMP over time.

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Details of the currently approved RMP:

Version number: 4.1

Approved with procedure: EMEA/H/C/004790/II/0009

Date of approval (opinion date): 27 FEB 2023

Other RMP versions under evaluation: Not applicable

QPPV signature:

EU QPPV name Dr. Jutta Pospisil

Contact person for this RMP [redacted]

E-mail address of contact person [redacted]

Electronic QPPV signature is attached at the end of the document.

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List of abbreviations

AD	Alzheimer's disease
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
AKR	Aldo-keto reductase
AMI	Acute myocardial infarction
AR	Androgen receptor
ARI	Androgen receptor inhibitor
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BID/b.i.d.	*Bis in die* (twice daily)
BP	Blood pressure
BS	Bone Scintigraphy
BSEP	Bile salt export pump
CBF	Cerebral blood flow
CI	Confidence interval
C_{max}	Peak concentration
COPD	Chronic obstructive pulmonary disease
CRPC	Castration-resistant prostate cancer
CT	Computed Tomography

CTCAE	Common terminology criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P450
DABE	Dabigatran etexilate
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
EAIR	Exposure-adjusted incidence rate
EAU	European Association of Urology
EBRT	External beam radiation therapy
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of treatment
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GLOBOCAN	Global Cancer Observatory
GnRHa	Gonadotropin-releasing hormone agonist
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HLGT	High Level Group Term

HLT	High Level Term
HR	Hazard ratio
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Nonproprietary Names
IQR	Inter quartile range
IV	Intravenous
LHRH	Luteinizing hormone-releasing hormone
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxic compound extrusion
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration sensitive prostate cancer
MDRD	Modification of Diet in Renal Disease
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	Metastatic hormone-sensitive prostate cancer
mPC	Metastatic prostate cancer
MRP2	Multidrug resistance-associated protein 2
MTD	Maximum tolerated dose
N	Number
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NEC	Not elsewhere classified

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NCI	National Cancer Institute
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NHANES	National Health and Nutrition Examination Surveys
nmCRPC	Non-metastatic castration-resistant prostate cancer
NTCP	Na^+-taurocholate cotransporting polypeptide
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall survival
PAM	Post authorisation measure
P-gp	Permeability glycoprotein
PK	Pharmacokinetic(s)
p.o.	Orally
PR	Interval on the ECG from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization)
PSA	Prostate-specific antigen
PT	Preferred Term
PV	Pharmacovigilance
PY	Person-years
qd	*Quaque die* (once a day)
QPPV	Qualified Person for Pharmacovigilance
QT	Interval on the ECG from the beginning of the QRS complex to the end

	of the T wave
QTc	Corrected QT interval
QTcB	Corrected QT (Bazett's formulae)
QTcF	Corrected QT (Fridericia's formulae)
RMP	Risk Management Plan
RP	Radical prostatectomy
RR	Relative risk
RT	Radiotherapy
SAE	Serious adverse event
SAF	Safety analysis set
SCR	Serum creatinine
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SHR	Sub-distribution hazard ratio
SOC	System Organ Class
SoC	Standard of care
SPM	Second primary malignancy
TEAE	Treatment-emergent adverse events
TESAE	Treatment-emergent serious adverse event
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit of normal

US	United States
UV	Ultraviolet

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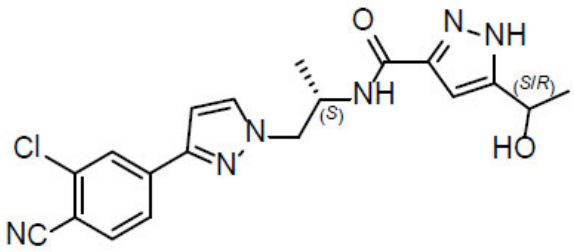
Part I: Product(s) overview

Part I: Product(s) overview

Table Part I.1 - Product(s) overview

Active substance(s) (INN or common name)	Darolutamide (INN)
Pharmacotherapeutic group(s) (ATC Code)	L02BB06
Marketing Authorisation Holder or Applicant	Bayer AG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	NUBEQA®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Darolutamide has the empirical formula of $C_{19}H_{19}Cl\ N_6O_2$ (Figure Part I.1) and the molecular weight of 398.85 g/mol. The chemical name is N-{(2*S*)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl] propan-2-yl}-5-[1-hydroxyethyl]-1H-pyrazole-3-carboxamide. Figure Part I.1: Chemical structure of darolutamide 
	Summary of mode of action: Darolutamide (BAY 1841788; ODM-201) is a novel non-steroidal selective androgen receptor antagonist with a flexible polar substituted pyrazole structure. The drug substance darolutamide is a 1:1 mixture of the two pharmacologically *in vitro* equally potent diastereoisomers (*S,R*)-darolutamide and (*S,S*) - darolutamide. Darolutamide has been shown to competitively inhibit androgen binding to the androgen receptor (AR) and inhibits AR nuclear translocation and interaction with DNA. The major metabolite of darolutamide is keto-darolutamide which has similar high binding affinity for the AR and exhibits comparable activity in *in vitro* assays. Darolutamide reduces prostate tumour cell proliferation leading to decreased tumour volume in mouse xenograft and orthotopic models of prostate cancer.

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Part I: Product(s) overview

	Important information about its composition: Nubeqa contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product.
Hyperlink to the Product Information	**Module 1.3.1**
Indication(s) in the EEA	nmCRPC (current): Treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. mHSPC (current): Treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy.
	mHSPC (proposed): Treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.
Dosage in the EEA	Current: The recommended dose is 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1,200 mg. Darolutamide should be continued until disease progression or unacceptable toxicity. Medical castration with a luteinising hormone-releasing hormone (LHRH) agonist or antagonist should be continued during treatment of patients not surgically castrated. *metastatic hormone-sensitive prostate cancer (mHSPC)* When used in combination with docetaxel in mHSPC patients, the first of 6 cycles of docetaxel should be administered within 6 weeks after the start of darolutamide treatment. The recommendation in the product information of docetaxel should be followed. Treatment with darolutamide should be continued until disease progression or unacceptable toxicity, even if a cycle of docetaxel is delayed, interrupted, or discontinued.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: White to off-white, oval, film-coated tablets, 300 mg.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indication: Metastatic hormone-sensitive prostate cancer (mHSPC)

Nubeqa is indicated for the treatment of adult men with mHSPC in combination with docetaxel and androgen deprivation therapy.

Metastatic hormone-sensitive prostate cancer (mHSPC), also known as metastatic castration sensitive prostate cancer (mCSPC), is defined as metastatic prostate cancer in patients who have not yet received or are continuing to respond to anti-hormonal therapy. mHSPC can occur due to recurrence after initial local treatment with surgery and/or radiotherapy, or as *de novo* disease mHSPC in patients whose first diagnosis of prostate cancer is metastatic disease (1).

SI.1.1 Incidence and prevalence

The overall incidence and prevalence of prostate cancer in general is presented in Section SI.2.1. Based on European country-specific registries, 5.2% to 17.8% of newly diagnosed prostate cancers are metastatic (2-5). Model-based simulation data in Italy estimated a prevalence of 33.9% for mHSPC and 66.1% for metastatic castration-resistant prostate cancer (mCRPC) as of 01 JAN 2019 (3).

In the US, nearly 8% of new cases with prostate cancer have metastases at diagnosis, i.e. *de novo* mHSPC (6). Moreover, the incidence of *de novo* mHSPC increased between 2011 and 2018 in men aged 45 to 74 years and 75 years or older, with an annual percentage change in the incidence of 5.3% and 6.5% per year, respectively (7).

SI.1.2 Demographics of the population and risk factors for the disease

The median age of presentation of *de novo* metastatic prostate cancer based on registry data is 73–76 years. Therefore, most men with mHSPC are in their mid-seventies when they are referred to an Oncology clinic (8). Further, elderly men may also be at a higher risk of relapse and prostate cancer-related death than younger men (9).

Within the mHSPC population, the influence of ethnic origin on clinical treatment outcomes is not known as for example in African-American patients that consistently have a higher incidence and mortality of prostate cancer compared with all other ethnic groups (incidence of 175.1 vs. 109.8 per 100,000 and mortality of 36.4 vs. 19.1 per 100,000) (10).

Although Black race/ethnicity has been associated with overall greater risk for prostate cancer, recent studies in castration-resistant prostate cancer (CRPC) have shown better outcomes for Black patients when treated with either docetaxel or abiraterone compared with white patients. For the mHSPC patient population, clinical trials leading to approval of docetaxel and abiraterone either did not report race or included a predominately white study population with <10% Black participants (10).

Clinical risk scores and genomic classifiers have been developed to identify cancer relapse and mortality risks, however the large majority of the patients included in the development and validation of these scores are <75 years of age, identifying a need for risk stratification tools to be studied in the geriatric population (9).

SI.1.3 The main existing treatment options

The treatment and management of patients with mHSPC has evolved over recent years with several new treatment options. Historically, for decades androgen deprivation therapy (ADT), achieved by surgical or medical castration, was the standard of care (SoC) for mHSPC (11). Starting in 2015, guidelines have recommended docetaxel in combination with ADT as SoC in both the US (2016) and European Union (EU) (2015) (12). In both the EU and the US, ADT in combination with one of the following is currently approved for the treatment of mHSPC: apalutamide and enzalutamide, androgen receptor inhibitors (ARI), darolutamide (with docetaxel), abiraterone, a Cytochrome P450 (CYP)17 inhibitor (with prednisone or prednisolone for high risk mHSPC in the US and for newly diagnosed high risk mHSPC in the EU). In the EU, docetaxel in combination with ADT, with or without prednisone or prednisolone is also approved for the treatment of mHSPC. Current systemic treatment options for patients with mHSPC are summarised in Table SI.1.

Both National Comprehensive Cancer Network (NCCN guidelines, prostate cancer, v.4 2024) and European Society for Medical Oncology (ESMO) guidelines (13) have been updated to recommend the 4 combination treatments in Table SI.1 for the initial treatment of mHSPC. Thus, any one of the 4 combinations can be considered as a SoC for patients with mHSPC although with variability of level of recommendation according to the specific guidelines.

Table SI.1: Systemic treatments for metastatic hormone-sensitive prostate cancer

Product(s) name	Mechanism of action	Relevant indication	First Approval year	Dose of product (in combination with ADT)	Efficacy[b]	Safety Most frequent ≥ Grade 3 AEs in product arm
Abiraterone acetate (ZYTIGA)	Androgen biosynthesis inhibitor (CYP17 inhibitor)	High risk mCSPC	2018 (US) 2017 (EU)	1,000 mg p.o. QD with 5 mg prednisone p.o. QD with ADT	**LATITUDE** (N=1,199) OS: HR=0.66 95% CI: [0.56; 0.78]	Hypertension (21%); Hypokalaemia (12%); ALT (5%) and AST (4%) increases
					STAMPEDE (N=1,917) OS: HR=0.63 95% CI: [0.52; 0.76]	Hypertension (5%); CV disorder (10%); hepatic disorder (7%)

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Table SI.1: Systemic treatments for metastatic hormone-sensitive prostate cancer

Product(s) name	Mechanism of action	Relevant indication	First Approval year	Dose of product (in combination with ADT)	Efficacy[b]	Safety Most frequent ≥ Grade 3 AEs in product arm
				1,000 mg p.o. QD with prednisone 5 mg p.o. QD with docetaxel 75 mg/m^2 IV 3 weekly for 6 cycles with ADT	**PEACE-1 (14)** (N=1,173) OS: HR=0.82 95% CI [0.69; 0.98]	Hypertension (22%); Neutropenia (10%); Hepatotoxicity (6%)
Darolutamide (NUBEQA)	2nd generation ARI	mHSPC	2022 (US) 2023 (EU)	600 mg p.o. BID with ADT and docetaxel	**ARASENS** (N=1,306) OS: HR=0.68 95% CI: [0.57; 0.8]	Neutrophil count decreased (23.2%); white blood cell count decreased (16.9%); neutropenia (8.6%)
Apalutamide (ERLEADA)	2nd generation ARI	mHSPC	2019 (US) 2019 (EU)	240 mg p.o. QD with ADT	**TITAN** (N=1,052) OS: HR=0.67 95% CI: [0.51; 0.89]	Rash (6%); asthenia (2%)
Enzalutamide (XTANDI)	2nd generation ARI	mHSPC	2019 (US) 2021 (EU)	160 mg p.o. QD with ADT 45% of patients also received early docetaxel in ENZAMET	**ARCHES** (N=1,150) OS: HR=0.81 95% CI: [0.53; 1.25]	Hypertension (3%)
					ENZAMET[c] (N=1,125) OS: HR=0.67 95% CI: [0.52; 0.86]	Hypertension (8%); neutropenia (6%); fatigue (6%); syncope (4%)

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Table SI.1: Systemic treatments for metastatic hormone-sensitive prostate cancer

Product(s) name	Mechanism of action	Relevant indication	First Approval year	Dose of product (in combination with ADT)	Efficacy[b]	Safety Most frequent ≥ Grade 3 AEs in product arm
Docetaxel (TAXOTERE)	Microtubule assembly inhibitor	mHSPC	2019 (EU) NA (US)[a]	75 mg/m^2 IV 3-weekly for 6 cycles with ADT	**STAMPEDE** N=1,776 OS HR=0.78 95% CI: [0.66 0.93]	Neutropenia (12%); febrile neutropenia (15%); General (7%) and GI disorder (8%)
					CHAARTED N=790 OS HR=0.72 95% CI: [0.59; 0.89]	Neutropenia (12%); febrile neutropenia (6%); fatigue (4%)

[a] Docetaxel is marketed and approved for mCRPC indication in the US. The use of docetaxel + ADT for the control arm in the ARASENS Study (Study 17777) was discussed and agreed by FDA.

[b] For additional information and final OS values refer to ARASENS Clinical Overview Section 6.1.2.

[c] In the ENZAMET trial, 45% of patients also received early docetaxel.

Overall survival analyses in this table are not adjusted for placebo crossing-over to study drug.

Source for efficacy and safety data (15).

Abbreviations: ADT = Androgen deprivation therapy; AE = Adverse event; ALT = Alanine aminotransferase; ARI = androgen receptor inhibitor; AST = Aspartate aminotransferase; BID: Bis in die (twice daily); CI = Confidence interval; CV = Cardiovascular; CYP = Cytochrome P450; EU = European Union; FDA = Food and Drug Administration (US); GI = Gastrointestinal; HR = Hazard ratio; IV: Intravenous; mCRPC = Metastatic castration-resistant prostate cancer; mCSPC = Metastatic castration sensitive prostate cancer; mHSPC = Metastatic hormone-sensitive prostate cancer; N = Number of patients; NA = Not applicable; OS = Overall survival; p.o. = Orally; QD = Once a day; US = United States.

Data from Phase 3 studies of available treatment options for patients with mHSPC were indirectly compared including ARI, a CYP17 inhibitor, or docetaxel combined with ADT (15). Even though comparison between the studies is challenging due to the differences in study populations, study designs, potential influence of geography, and the time-period in which the studies were conducted, the conclusion was that treatment choice is based upon the specific characteristics of each patient.

SI.1.4 Natural history of the indicated condition in the untreated population, including mortality and morbidity

De novo or newly diagnosed mHSPC (patients whose first diagnosis of PC is metastatic disease) is recognised as an aggressive form of the disease with rapid progression to the metastatic castration-resistant state in virtually all patients (16).

Although almost all men with mHSPC initially experience a response to ADT, most will develop mCRPC within 1 to 3 years of their diagnosis (17).

For patients with localised prostate cancer, the survival rate at 5 years is almost 100%. However, for patients with metastatic prostate cancer (mPC) in which the prostate cancer has spread to distant parts of the body (lymph nodes, bones, other organs), the survival rate at 5 years is only about 30% (18). The survival times are limited in patients with mHSPC (range 30-60 months depending on the volume of disease).

SI.1.5 Important comorbidities

There is no data available specifically for mHSPC. Overall, most men with mHSPC are in their seventies when they are referred to an Oncology clinic and a sizeable portion will have a few comorbidities, some of which may are likely to limit life expectancy more than prostate cancer, and therefore have competing risks of mortality (8).

SI.2 Indication: Non-metastatic castration-resistant prostate cancer (nmCRPC)

Nubeqa is indicated for the treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.

Prostate cancer is the second most frequent cancer diagnosed in men and the 8th leading cause of death in the world (19). Prostate cancer commonly affects middle-aged men. It typically presents clinically after the age of 50 years and takes more than 25 years to develop from a local lesion to a malignant phenotype. Secondary prevention through prostate-specific antigen (PSA) analyses and prostate biopsies have dramatically increased incidence during the preclinical period. This preclinical period offers the potential for cancer suppression and inhibition of progression rather than just prevention (20).

Since the seminal work of Huggins and Hodges in 1941, prostate cancer has been recognised as an androgen-sensitive disease, because the cancer growth is dependent on androgen-stimulating proliferation (21). Androgens act through the androgen receptor (AR). The structure of the AR is similar to other steroid receptors with modular structure, a central deoxyribonucleic acid (DNA)-binding domain, amino-terminal transcriptional activation domain, and carboxy-terminal ligand-binding domain (22). Both, testosterone and dihydrotestesterone bind to the AR, inducing translocation of the androgen-AR homodimer from the cytosol to the nucleus where it binds to specific DNA sequences, and stimulates transcription of androgen-regulated genes. The best-known androgen-regulated gene encodes PSA.

Prostate cancer progression to malignancy usually occurs during andropause, when testosterone levels fall relatively to those of estradiol and the oestrogen/androgen ratio can increase up to 40% (23). Because of PSA utilisation in screening for prostate cancer, an increasing number of patients are diagnosed at an early stage and receive local treatments, including surgery and radiation. Recurrence of disease in these patients, as suggested by increasing PSA levels, is usually treated with ADT (24). ADT comprises either surgical castration or chemical castration using luteinising hormone-releasing hormone analogues

(25). Early in its development, prostate cancer requires relatively high levels of androgens and is referred to as androgen-dependent or androgen-sensitive, because treatments that decrease or block androgen levels can inhibit their growth (26). A significant fraction of men with androgen-sensitive prostate cancer develops CRPC.

CRPC tumours have been thought to be independent of AR signalling for tumour growth. However, findings suggest that AR signalling persists in many castration-resistant tumours (27-29). CRPC is commonly associated with an increased expression level of the AR gene, which suggests that the tumour growth is still dependent on androgen signalling, where androgens from tumoral sources may fuel the growth. Increased AR expression can occur through amplification of the AR gene, mutations in AR, or other mechanisms (30, 31). Analysis of CRPC tissue from patients shows that AR amplification occurs in 20% to 30% of cases (32, 33). As a consequence, even very low levels of testosterone and/or dihydrotestosterone might cause androgen signalling (34).

NmCRPC represents a transitional disease state which is defined by increases in PSA levels despite castration levels of androgens during ADT in the absence of clinically metastatic disease (35).

SI.2.1 Incidence and prevalence

There is limited information about the epidemiology of nmCRPC. A systematic review on the prevalence of CRPC includes five out of ten studies that evaluate the prevalence of CRPC (36). This systematic review estimates a 10% to 20% prevalence of CRPC over a 5-year period, utilising the reports that define CRPC by a rise in PSA levels following castration. Approximately 16% of individuals diagnosed with CRPC did not present any evidence of metastatic disease, and 33% went on to develop metastases within two years of their CRPC diagnosis. The median survival following a diagnosis of CRPC was 14 months (36). These limited data do not allow an evaluation of the effect of treatment pathways or metastasis on the time to castration-resistance after initiation of ADT.

According to the most recent Global Cancer Observatory (GLOBOCAN) estimates, there were an estimated 1,468 million new cases of prostate cancer in 2022, ranking prostate cancer as the second most frequent cancer after lung cancer in men (37). According to these estimates, prostate cancer is the most frequently diagnosed cancer among men in almost two thirds (118 of 185) of the world's countries, with the highest rates seen in Northern Europe, Australia/New Zealand, the Caribbean, and Northern America. Prostate cancer is the leading cause of cancer death among men in 52 countries, including many countries in the Caribbean and sub-Saharan Africa, in Central and South America (e.g., Ecuador, Chile, and Venezuela), as well as Sweden in Europe. GLOBOCAN data on prostate cancer incidence and prevalence in European countries are presented in Table SI.2.

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Table SI.2: Age-standardised incidence and prevalence of prostate cancer in Europe, for 2022 (37)

Country	Annual Incidence		Prevalence per 100,000 men		
	Number of cases	Rate per 100,000	1-year	3-year	5-year
Albania	419	12.2	19.5	45.7	61.2
Austria	5,934	61.0	125.5	358.8	564.7
Belarus	4,972	68.2	96.3	277.5	439.8
Belgium	10,523	81.7	173.3	492.3	770.5
Bosnia and Herzegovina	922	24.5	41.1	100.5	138.6
Bulgaria	3,122	38.2	78.2	219.6	340.3
Croatia	3,247	69.5	144.6	410.8	642.8
Cyprus	691	60.9	102.2	288.4	448.8
Czechia	7,956	70.0	139.6	399.1	627.7
Denmark	5,250	76.7	174.4	493.8	770.7
Estonia	1,174	98.8	172.1	495.3	783.6
Finland	5,930	82.2	206.8	581.8	902.3
France	57,357	82.3	167.7	479.1	753.4
Germany	65,269	54.2	150.5	417.8	639.7
Greece	7,036	51.4	125.5	350.8	540.2
Hungary	6,660	68.5	128.0	364.7	572.1
Iceland	221	65.6	124.5	355.5	557.7
Ireland	4,216	99.8	166.9	481.5	763.9
Italy	38,180	49.5	118.3	334.2	520.5
Latvia	1,662	97.3	173.6	497.3	783.5
Lithuania	3,208	135.0	237.9	689.8	1,100.1
Luxembourg	443	74.7	128.0	363.6	570.3
Malta	284	50.4	117.1	329.8	513.8
Montenegro	220	36.1	60.2	168.4	261.5
North Macedonia	790	41.4	54.3	135.2	189.6
The Netherlands	11,956	57.0	135.3	384.9	602.6
Norway	6,276	109.9	221.3	630.9	990.4
Poland	22,480	56.0	110.8	313.7	489.4

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Table SI.2: Age-standardised incidence and prevalence of prostate cancer in Europe, for 2022 (37)

Country	Annual Incidence		Prevalence per 100,000 men		
	Number of cases	Rate per 100,000	1-year	3-year	5-year
Portugal	7,529	62.6	138.0	390.2	608.6
Republic of Moldova	985	34.6	36.4	91.5	129.6
Romania	10,442	53.9	95.9	272.8	427.2
Russian Federation	52,712	47.4	66.5	190.9	301.7
Serbia	3,398	37.0	66.4	189.0	296.1
Slovakia	3,606	69.2	120.3	343.4	539.7
Slovenia	1,765	72.6	161.0	460.0	723.6
Spain	32,967	66.5	134.0	384.1	606.0
Sweden	11,732	104.3	222.3	632.4	990.9
Switzerland	6,871	69.1	153.9	436.7	682.8
Ukraine	9,254	26.4	33.4	83.3	116.7
United Kingdom	55,485	74.0	155.9	440.7	686.9

For Germany, the Robert Koch Institute reports that the age-standardised incidence rate in 2014 was 92.7 per 100,000 men (38). It was estimated that this rate will be the same in 2018, with 57,370 new prostate cancer cases in 2014 and 60,700 new cases in 2018, respectively. The 5- and 10-year prevalence were estimated at 271,800 and 494,800 cases, respectively.

The 2017 analysis of the US National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Programme estimated that 3,085,209 men were living with prostate cancer in the US (39) in 2014. The age-adjusted incidence rate for prostate cancer was 119.8 per 100,000 men per year for the period of 2010-2014. Of the newly diagnosed prostate cancer cases, 79% were diagnosed at the local stage, 12% at the regional stage, 5% at metastatic stage, and 4% were unstaged. A total of 161,360 incident cases were estimated for 2017, accounting for 9.6% of all new cancer cases.

In Canada, the Canadian Cancer Society reported that the age-standardised incidence rate has been declining since 2007 at a rate of 5.3% per year. The estimated prostate cancer incidence was 110.4 per 100,000 men for 2017 (40).

In Australia, Cancer Australia reported that approximately 19,993 men were newly diagnosed with prostate cancer in 2011 and approximately 86,207 men were living with a diagnosis of prostate cancer in 2009 (diagnosed in the 5-year period of 2005 to 2009). The age-

standardised incidence rate was 167 cases per 100,000 males. In 2015, it was estimated that the age-standardised incidence rate would be 126 cases per 100,000 males (41). An analysis of 2,724 prostate cancer cases from the Prostate Cancer Registry of Victoria region of Australia between 2008 and 2011 was performed. It showed that the vast majority of these cases were diagnosed with localised disease and only 3.3% were diagnosed with metastatic disease (42).

A study of 12 African population-based registries (43) showed that the incidence rates among Black Africans were highest in the East (10.7-38.1 per 100,000 man-years, age-adjusted world standard) and lowest in the West (4.7-19.8). These rates were considerably lower than those of 80.0-195.3 per 100,000 observed among African-Americans, which the authors attribute to differences in medical care access, screening, registry quality, genetic diversity, and Westernisation (43).

As per the International Agency for Research on Cancer, the estimated incidence rates of prostate cancer in 2012 for Eastern and South-Central Asia were 28.5 and 5.2 per 100,000 men, respectively (37). In Japan, the Foundation for Promotion of Cancer Research reported an estimated incidence of prostate cancer cases in 2016 of 92,600 men, accounting for 16% of all new cancer cases in men (44). The Korean National Cancer Centre reported an incidence rate for prostate cancer of 36.8 per 100,000 men in 2012, accounting for 8.2% of all incident cancer cases in men (45). An analysis of several population-based cancer registries in China by the National Central Cancer Centre of China lead to an estimated total incidence of prostate cancer of 60,300 cases in 2015 (46).

SI.2.2 Demographics of the population and risk factors for the disease

Currently, no data is available pertaining to the demographics and risk factors specifically for nmCRPC.

The risk of prostate cancer increases with age. According to the most recent NCI SEER cancer statistics review (39), prostate cancer is most frequently diagnosed among men between 55 and 74 years old (see Table SI.3), with a median age of diagnosis at 66 years.

Table SI.3: Percent of new prostate cancer cases by age group in the US (39) from 2011-2015

Age (years)	Proportion (%)
<45	0.5
45-45	9.0
55-64	32.7
65-74	38.8
75-84	15.1
84	3.9

SEER Cancer Statistics Review 2011-2015
Abbreviations: SEER = Surveillance, Epidemiology, and End Results, US = United States.

Prostate cancer risk is positively associated with a family history of prostate cancer. In a prospective cohort study from the United Kingdom (UK) by Perez-Cornago *et al*. (47) of 219,335 men, a family history of prostate cancer was associated with a hazard ratio (HR) of 1.94, (95% confidence interval [CI], 1.77-2.13). Randazzo *et al*. (48) analysed prostate cancer incidence in 4,932 Swiss men undergoing PSA testing every 4 years, where 334 of those men had a positive prostate cancer family history. Cumulative prostate cancer incidence was 18% in the subjects with a positive family history and 12% in those without family history, corresponding to an odds ratio of 1.6 (95% CI, 1.2-2.2; p=0.001).

Black ethnicity is another important risk factor for developing prostate cancer in the US. Park *et al*. (49) report the results of a prospective cohort study from the US with 19,833 White, 9,284 Black, 5,454 native Hawaiian, 23,687 Japanese-American, and 16,958 Latino men. Compared to White males, Black and Latino men had increased age- and risk factor-adjusted rate ratios of 2.08 (95% CI, 1.93-2.25) and 1.16 (95% CI, 1.07-1.26), respectively. In the prospective cohort study conducted by Perez-Cornago *et al*. (47) in the UK with 205,839 White, 1,077 mixed, 5,765 Asian, 3,279 Black, and 1,926 men of other ethnicity, the HR for Black vs. White ethnicity was 2.61 (95% CI, 2.10–3.24), with no other ethnic group having an increased risk, as compared to Whites.

Table SI.4 presents the age-adjusted incidence rates of prostate cancer by race in the US as reported by NCI in 2018 (39).

Table SI.4: Prostate cancer incidence by race/ethnicity (39)

Race/ethnicity	Incidence per 100,000
All Races	112.6
White	105.7
Black	178.3
Asian/Pacific Islander	59.1
American Indian/Alaska Native	54.8
Hispanic	91.8
Non-Hispanic	116.1

SEER Cancer Statistics Review 2011-2015, Age-adjusted.
Abbreviations: SEER = Surveillance, Epidemiology, and End Results.

In the above-mentioned studies by Park *et al*. (49) and Perez-Cornago *et al*. (47), no lifestyle factors associated with an increased risk were identified. Only smoking (≥20 cigarettes per day vs. never-smoking) and diabetes were associated with a reduced risk.

SI.2.3 The main existing treatment options

Until 2018, the secondary hormone treatments (*e.g.*, nonspecific steroidal biosynthesis inhibitors or antiandrogenes bicalutamide or nilutamide) were used off-label in non-metastatic

setting. Therefore there was an unmet need for treatments options for non-metastatic (M0) prostate cancer, where delaying the time to disease progression is most important (50).

Enzalutamide and apalutamide were approved for the treatment of nmCRPC. Both of these novel agents inhibit AR ligand binding and thus AR translocation to the nucleus and DNA-binding (51, 52). Enzalutamide was initially approved for the treatment of metastatic CRPC. In 2018, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) decided to expand approval for nmCRPC (53, 54). Apalutamide is a new drug which was approved by FDA for treatment of patients with nmCRPC in 2018 (53). Additionally, the Committee for Medicinal Products for Human Use adopted a positive opinion in 2018, recommending the granting of a marketing authorisation for enzalutamide and apalutamide in EU.

SI.2.4 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Mortality data for nmCRPC is limited. Among 201 nmCRPC patients from the placebo group of an aborted randomised controlled trial at the 2-year mark, 33% of subjects had developed at least one bone metastasis at 2 years, 21% had died, and 42% had experienced a bone metastasis and/or had died (55). Median bone metastasis-free survival was 907 days.

Baseline PSA level greater than 10 ng/mL (relative risk, 3.18; 95% CI, 1.74-5.80; $p<0.001$) and PSA velocity (4.34 for each 0.01 increase in PSA velocity; 95% CI, 2.30-8.21; $p<0.001$) independently predicted shorter time to first bone metastasis. Baseline PSA and PSA velocity also independently predicted overall survival and metastasis-free survival.

A Gleason score >7 was not significantly associated with bone metastasis-free survival (55).

Though there is limited data on the natural history of nmCRPC, there is a lot on prostate cancer.

The 2022 GLOBOCAN estimates rank prostate cancer as the 8th leading cause of cancer death in men, 397,430 associated deaths worldwide (19).

While PSA screening is associated with higher prostate cancer incidence, it is also associated with reduced prostate cancer mortality. In a prospective population-based cohort study in Sweden (56) with 7,647 men who had PSA screening performed over the course of 18 years and 9,949 who did not, cumulative prostate cancer incidence was 14% in the screening group, compared to 9.7% in the control group. Cumulative prostate cancer mortality was 0.98% (95% CI, 0.78-1.22%) in the screening group versus 1.50% (95% CI, 1.26-1.79%) in controls, presenting an absolute reduction of 0.52% (95% CI, 0.17-0.87%).

A diagnosis of prostate cancer that is localised or regional carries a lower risk of mortality from the disease compared to cancer metastasised to distant sites. In the US, the (2007-2013) 5-year survival rate was 100.0% for localised and regional prostate cancer, respectively, but 29.8% for metastatic prostate cancer. The overall 5-year survival rate was 98.6%, with an annual mortality due to prostate cancer of 20.1 per 100,000 men (39). Approximately 70% of prostate cancer deaths occur in persons older than 75, with the median age of mortality being 80 years.

US age-adjusted mortality rates of prostate cancer by race, based on 2011-2015 SEER data (39), are provided in Table SI.5. Mortality is particularly high in Black men.

Table SI.5: Age-adjusted prostate cancer mortality by race/ethnicity in the US (39)

Race/ethnicity	Number of deaths per 100,000
All Races	19.5
White	18.2
Black	39.9
Asian/Pacific Islander	8.8
American Indian/Alaska Native	19.8
Hispanic	16.2
Non-Hispanic	19.8

SEER Cancer Statistics Review 2011-2015, Age-adjusted.
Abbreviations: SEER = Surveillance, Epidemiology, and End Results, US = United States.

According to the Canadian Cancer Society, most prostate cancer deaths occur in men aged 80 years or older. In 2017, the estimated age-standardised mortality rate for prostate cancer was 23.8 per 100,000 (40).

The Eurostat 2020 report (57) states that 68,900 men died from prostate cancer in the EU in 2020, equivalent to 10.6% of all deaths from cancer and 2.6% of the total number of male deaths from any cause. Among the EU Member States, the percentage of all deaths among men that was attributed to prostate cancer was as low as 1.6% in Romania and 1.8 % in Malta and Bulgaria, but with much higher shares in Sweden (4.5 %), Norway (4.9%) and Denmark (4.9 %). The EU standardised death rate for prostate cancer was 36.2 per 100,000 male inhabitants. Some of the highest standardised death rates for prostate cancer in 2020 were recorded across the Nordic and Baltic Member States, with peaks above 50.0 per 100,000 male inhabitants recorded for all three Baltic Member States, two of the Nordic Member States (Denmark and Sweden), as well as Slovenia, Croatia and Slovakia. Rates of less than half that level were reported by southern EU Member States – Cyprus, Spain, Italy and Malta – that reported death rates for prostate cancer below 30.0 per 100,000 male inhabitants, and the lowest rate was in Malta (23.0 per 100,000 male inhabitants).

GLOBOCAN estimates for 2022 mortality in European countries are provided in Table SI.6 (19, 37).

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Table SI.6: Age-standardised mortality due to prostate cancer in Europe in 2022 (19, 37)

Country	Number of cases	Rate per 100,000
Albania	174	5.3
Austria	1,372	9.5
Belarus	1,134	15.4
Belgium	1,902	10.1
Bosnia and Herzegovina	457	11.8
Bulgaria	1,302	13.7
Croatia	908	15.5
Cyprus	195	14.2
Czechia	1,622	11.1
Denmark	1,381	14.6
Estonia	352	21.7
Finland	932	9.8
France	9,264	8.2
Germany	18,015	11.6
Greece	1,945	8.9
Hungary	1,554	13.7
Iceland	68	14.0
Ireland	592	9.9
Italy	8,196	6.6
Latvia	471	22.2
Lithuania	545	17.2
Luxembourg	62	7.8
Malta	55	7.7
Montenegro	91	13.7
North Macedonia	272	13.7
The Netherlands	3,258	11.4
Norway	1,116	13.9
Poland	7,823	17.3
Portugal	2,083	11.1
Republic of Moldova	373	13.4

Table SI.6: Age-standardised mortality due to prostate cancer in Europe in 2022 (19, 37)

Country	Number of cases	Rate per 100,000
Romania	2,854	12.3
Russian Federation	14,635	12.7
Serbia	1,197	11.4
Slovakia	944	16.9
Slovenia	483	14.8
Spain	6,217	7.6
Sweden	2,475	13.4
Switzerland	1,472	9.9
Ukraine	4,166	11.4
United Kingdom	13,237	11.8

The Japanese Foundation for Promotion of Cancer Research estimated that 12,300 deaths due to prostate cancer occurred in 2016, accounting for 6% of all cancer deaths in men (44). For Korea, the National Cancer Centre reports that 3.5% of all 47,079 cancer deaths in men, occurred due to prostate cancer (45). In China, the estimated number of deaths due to prostate cancer in 2015 was 26,600 (46).

SI.2.5 Important comorbidities

No data are available specifically for nmCRPC. Baik *et al*. (58) report results of an observational cohort study using the US Medicare beneficiaries database: in a cohort of 440,129 men newly diagnosed with prostate cancer (mean age ± standard deviation [SD] 76.36 ± 6.35 years) the mean number of comorbid conditions prior to ADT initiation was 4.70.

It must be taken into account that nmCRPC patients were already exposed to ADT before castration-resistance occurred; these patients are therefore more likely to have a medical history of conditions which are more frequent with ADT use.

Alzheimer's disease (AD), dementia, cardiovascular disorders, osteoporosis, rheumatoid arthritis/osteoarthritis, a history of fractures or falls, anaemia, diabetes, hyperlipidaemia, chronic kidney disease, depressive disorders, urinary incontinence, erectile dysfunction, a history of seizure, cataract, glaucoma, chronic obstructive pulmonary disease (COPD), and asthma are considered important comorbidities in the target population. Further details are provided below.

Alzheimer's disease (AD) and dementia

The above-mentioned observational cohort study conducted by Baik *et al.* (58) included 1.2 million prostate cancer patients, thereof 440,129 treated with ADT and 798,750 not treated with ADT. Patients with AD, dementia, or stroke (not specified) prior to the diagnosis of prostate cancer were excluded. Of the 1.2 million patients, 109,815 (8.9%) developed AD and 223,765 (18.8%) developed dementia. Patients with ADT treatment had no increased risk of AD (sub-distribution hazard ratio [SHR] (59), 0.98; 95% CI, 0.97-0.99) and had only a miniscule risk of dementia (SHR, 1.01; 95% CI, 1.01-1.02).

Cardiovascular disorders

The ADT-associated changes in body composition, lipids, and insulin sensitivity are suspected to increase the risk for diabetes and cardiovascular disorders in prostate cancer patients. The overall evidence is, however, conflicting and the relationship between ADT and cardiovascular disorders remains unclear (60).

In the study by Baik *et al.* (58), acute myocardial infarction (AMI) was present in 3.39% of the 440,129 ADT-treated patients (mean age ± SD: 76.36 ± 6.35 years) at baseline, atrial fibrillation in 11.47%, heart failure in 18.19%, ischaemic heart disease in 43.04%, and hypertension in 65.51%. In this study, patients with stroke (not specified) diagnosed prior to the diagnosis of prostate cancer were excluded.

Similar point prevalences for cardiovascular comorbid conditions were found by Chen *et al.* (61) in a cohort of 11,137 prostate cancer patients (median age ± interquartile range 75.00 ± 11.00 years) identified in the nationwide Taiwanese Health Insurance Research Database, prior to treatment with gonadotropin-releasing hormone agonist (GnRHa): 1.43% had a history of myocardial infarction, 6.02% had a history of ischaemic stroke, 1.72% had a history of atrial fibrillation, 1.66% had a history of heart failure, 34.83% had a history of coronary artery disease,3.10% had prior percutaneous coronary intervention, and 66.18% had a history of hypertension.

Haque *et al.* (59) published results of a prospective cohort study in the US. A total of 7,637 patients diagnosed with localised prostate cancer, 2,170 of whom used ADT during the course of the study, were followed up for a median of 3.4 years. Of the 2,170 patients who were exposed to ADT (80.2% of whom were aged >65 years), 22.5% had cardiovascular disease at baseline and 63.6% had hypertension. Crude incidence rates of cardiovascular disease per 1,000 person-years (PY) were 18,47 for AMI, 2.52 for cardiac arrest, 3.06 for stroke (not specified), 23.38 for arrhythmia, 2.39 for angina (not specified), 32.42 for heart failure, 2.13 for cardiomyopathy, 3.59 for conduction disorder, 2.92 for valvulopathy, and 0.13 for hypertensive heart disease.

Bone disorders, fractures, and falls

In the cohort studied by Chen *et al.* (61), osteoporosis was present at baseline in 6.02% of the patients who received GnRHa. Baik *et al.* (58) report baseline point prevalences of 2.37% and 30.90% for osteoporosis and rheumatoid arthritis/osteoarthritis, respectively.

Beebe-Dimmer *et al*. (62) conducted a retrospective US population-based cohort study using the SEER-Medicare database which links SEER registry data to Medicare enrolment and claims files. The study included 80,844 patients aged ≥66 years, thereof 72,392 with non-metastatic prostate cancer, 49.9% of whom received ADT. The fracture rate among patients receiving at least one dose of GnRHa was 57 per 1,000 PY (95% CI, 56-58), compared with 31 per 1,000 PY (95% CI, 30-32) among non-users. The fracture rate among orchiectomy patients was 76 per 1,000 PY (95% CI, 68-84). The risk of experiencing fractures was positively associated with the cumulative ADT dose and inversely related to the number of months since last use. The three most common sites of first-time fracture among patients in the study were rib (17.5%), hip (16.5%), and spine (14.6%).

In a population-based, retrospective cohort study in Taiwan employing the Taiwan Longitudinal Health Insurance Database 2005 with 886 prostate cancer patients (mean age ± SD: 74.2 ± 8.4 years), Wu *et al*. (63) identified an incidence rate of falls of 13.37 per 1,000 PY (95% CI, 9.15-18.88).

Anaemia

Hicks *et al*. (64) used the UK Clinical Practice Research Datalink, a database comprising longitudinal records of over 14 million patients from over 700 general practices, linked to the Hospital Episode Statistics repository, to conduct a population-based study. A total of 10,364 prostate cancer patients aged >40 years were included, with 15,872 PY for non-ADT use, 9,755 PY for ADT use at the time point of incident anaemia, and 5,948 PY for ADT use prior to but not at the time point of incident anaemia. Anaemia incidence rates were 23.5 vs. 5.9 per 100 PY in ADT vs. non-ADT subjects. In the study by Baik *et al*. (58), 33.56% of the patients who subsequently received ADT had a diagnosis of anaemia at baseline.

Metabolic diseases

Among the ADT-treated patients in the studies by Baik *et al*. (58), Chen *et al*. (61), and Haque *et al*. (59), diabetes baseline point prevalences ranged from 20.3% to 26.09%. Baik *et al*. and Chen *et al*. also report hyperlipidaemia baseline point prevalences of 55.77% and 34.13%, respectively.

Chronic kidney disease

Chronic kidney disease was present at baseline in 12.09% and 12.13% of the patients in the cohorts studied by Baik *et al*. (58) and Chen *et al*. (61), respectively.

Depressive disorders

Among the prostate cancer patients who received ADT in the study by Baik *et al*. (58), 8.13% had a diagnosis of depression at baseline. Incident depressive disorders are more frequent in prostate cancer patients who receive ADT:

In a retrospective population-based cohort study in the US with 33,882 men with localised prostate cancer (mean age 73.5 years) identified in the SEER-Medicare database, the cumulative incidence of depression increased from 6.1% to 7.6% to 8.0% with ≤6, 7 to 11, and ≥12 months of ADT, respectively (65).

In a nationwide population-based retrospective cohort study using the Taiwan Health Longitudinal Insurance database 2005 (66) with 868 prostate cancer patients who received ADT (mean age 74.1 years) and 846 who did not (mean age 70.4 years), the incidence of depressive disorders per 1,000 PY was 13.9 (95% CI, 9.5-19.6) in the ADT group and 6.7 (95% CI, 3.7-11.0) in the non-ADT group, with an adjusted HR for ADT recipients of 1.93 (95% CI, 1.03-3.62; p≤0.05).

Urinary incontinence and erectile dysfunction

The presence of urinary incontinence was analysed in an US-population-based retrospective cohort study utilising the publicly available data from the 2001 to 2010 National Health and Nutrition Examination Surveys (NHANES), including 136 prostate cancer patients (mean age 70.4 years) who had radical prostatectomy (RP), 125 (mean age74.2 years) who had radiotherapy (RT), 55 (mean age 69.8 years) who had both treatments, and 3,534 non-prostate-cancer controls (mean age 68.8 years) (67). Urinary incontinence was reported by 26.0% (95%CI, 24.3-27.7) of the men in the control group, 57.4% (95% CI, 45.4-68.7) of the RP patients, 42.6% (95% CI, 32.9-53.0) of the RT patients, and by 80.7% (95% CI, 65.1-90.3) of the RP plus RT patients.

A Danish retrospective cohort study assessed erectile function 12 months after RP in 704 prostate cancer patients (median age ± SD: 62 ± 5.8 years) identified by a medical record review (68). Of the 704 men, 226 (32.1%) reported to have erection sufficient for intercourse, 109 (48.2%) of these 226 men required erectile aids. Erectile dysfunction was reported by 478 men (67.9%) and of those by 121 (25.3%) despite the use of erectile aids.

Seizure

Treatment with enzalutamide and apalutamide is known to be associated with increased risk for seizures (69, 70). Epidemiological data is only available for metastatic CRPC patients from a retrospective cohort study with 3,927 patients selected from MarketScan Commercial and Medicare Supplemental Databases (71). Overall, seizure incidence in this population was 1.8 per 100 PY. The most common risk factors were history of seizure threshold lowering medication use (35%), history of loss of consciousness (6%), history of transient ischaemic attack or cerebrovascular accident (2%), treated brain metastasis (0.9%), history of seizure (0.6%), and dementia (0.5%). The incidence of seizure was higher among patients with at least one risk factor (2.8 per 100 PY) than among those without risk factors (1.2 per 100 PY).

Ocular disorders

In the above-mentioned cohort study by Baik *et al*. (58), cataract was present in 52.74% and glaucoma in 16.53% of the 440,129 ADT-treated patients (mean age ± SD: 76.36 ± 6.35 years) at baseline.

Respiratory tract disorders

Baik *et al*. (58) report baseline point prevalences of 17.87% and 5.73% for COPD and asthma, respectively.

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity:	
Acute toxicity studies were not conducted. Results from repeat-dose toxicity studies in male and female rats (up to 6 months) and male and female dogs (up to 9 months) revealed the male reproductive system as main target for reversible atrophic changes. Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy and secretory reduction in seminal vesicles and mammary glands in rats as well as testicular hypospermia, seminiferous tubule dilatation and degeneration in dogs. No treatment-related effects were observed in female rats and dogs.	The findings in rats and dogs are directly related to the desired beneficial anti-androgenic mode of action, are not considered as adverse and are not considered to pose a risk for prostate cancer patients. Prolonged exposure of healthy males to darolutamide is not indicated since their sexual function might become reversibly impaired as a known class effect of anti-androgenic drugs.
Reproductive and developmental toxicity studies were not conducted. On the basis of the results from the repeat-dose toxicity studies and as a consequence of the anti-androgenic mode of action, genital malformations (feminisation) and impairment of later fertility for male foetuses is to be expected if pregnant mothers are exposed during the sensitive phase of development.	Since the current indications are restricted to the treatment of prostate cancer, women of childbearing potential are not indicated for treatment. In principle the risk for the development of male foetuses applies also to human usage during pregnancy (from about day 40 after conception onwards).
Overall, the results from *in vitro* and *in vivo* genotoxicity studies do not indicate a relevant genotoxic risk to humans.	On the basis of the lack of genotoxicity, the demonstrated lack of cytotoxicity or proliferating effects in the repeat-dose toxicity studies and on the experience with other members of the class of anti-androgenic drugs, no risk of genotoxicity is anticipated for darolutamide.
No carcinogenicity studies were originally conducted in accordance with the recommendations in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guideline since the proposed indication is for advanced cancer. The carcinogenic potential of darolutamide was studied in a 26-week study in transgenic RasH2	In the transgenic mouse model, darolutamide did not show a carcinogenic potential in the range of the exposure in humans at the therapeutic dose of 600 mg BID. Higher doses could not be tested because of exposure saturation. Based on this study carcinogenic risk of darolutamide cannot be completely excluded. Carcinogenicity potential is categorised as **an Important potential risk.**

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
mice. Dose selection was based on an initial 7-day pilot study evaluating the toxicokinetics of darolutamide and a subsequent 4-week dose-range-finding study in 001178-W (wild type) RasH2 mice. In the 4-week study, the toxicokinetic profile was evaluated including the systemic exposure of darolutamide, its stereoisomers and its major metabolite keto-darolutamide. The high dose of 500 mg/kg BID (8 hours apart) represents the limit dose for systemic toxicity studies and resulted in exposure saturation. This dose was well tolerated without signs of toxicity. In the pivotal 26-week study with orally administered darolutamide in 001178-T (hemizygous) RasH2 mice, no darolutamide-related effects were noted on the incidence or type of neoplasms observed. The achieved C_{max} concentrations were in the range of the C_{max} in humans at the therapeutic dose of 600 mg BID. In conclusion, no carcinogenic potential was observed up to the highest darolutamide dose administered.	
Safety pharmacology	
In rats, darolutamide had no biologically relevant effects on the central nervous system and respiratory function.	Not applicable.
After single intravenous administration of darolutamide to anesthetised dogs, vasodilation, associated with a decrease in arterial blood pressure (BP), was observed at high plasma concentrations of darolutamide. In conscious dogs, investigated within the frame of systemic toxicity studies, no effects on arterial BP were observed after oral administration of darolutamide.	Decrease in arterial BP observed in anesthetised dogs is not regarded to be of physiological relevance to humans at clinically relevant plasma concentrations as this effect was observed at high systemic plasma exposure levels and could not be confirmed in conscious animals.
Studies to address the risk of darolutamide for QT prolongation in humans were performed *in vitro* (human ether-à-go-go-related gene [hERG] K^+ channel and L-type Ca^{2+} voltage clamp assays) and *in vivo* (QT/corrected QT [QTc] intervals in electrocardiogram [ECG] recordings of Beagle dogs). The hERG K^+ and L-type Ca^{2+}	There is no evidence that darolutamide has potential for delaying repolarisation.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
currents were only blocked at very high concentrations that are not regarded to be of physiological relevance. In anaesthetised dogs, darolutamide slightly decreased the QT interval duration, but this effect was not found in conscious dogs.	
Mechanisms for drug interactions	
Studies to address the drug-drug interaction (DDI) potential of darolutamide towards several cytochrome P450 (CYP) and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes were performed *in vitro*. CYP3A4, aldo-keto reductase (AKR), and UGT enzymes are primarily involved in the metabolism of darolutamide. Darolutamide is a weak inhibitor of all CYP enzymes with the lowest half-maximal inhibitory concentration (IC_{50}) value for CYP2C9 (30 µM). The major metabolite keto-darolutamide shows similar CYP inhibition properties. Applying the mechanistic static model approach as suggested by the Food and Drug Administration (FDA) revealed that no DDIs with substrates of CYP2C9 will have to be expected *in vivo* and therefore also for no other CYP substrate. Darolutamide is an inhibitor of UGT1A9 and 1A1, lowest inhibition constant of 6.3 µM for 1A9. In view of the low therapeutic unbound plasma concentrations, the risk for clinically relevant DDIs with co-administered drugs primarily cleared by the UGT isoforms is considered low.	Co-administered drugs which are CYP3A4 inhibitors may cause an increase of darolutamide exposure. Therefore, a clinical study was conducted (Study no. 17726, see clinical part). For AKR and UGT enzymes, no clinically relevant inhibitors are known. *In vitro* experiments indicate a low risk for DDIs resulting from inhibitory effects of darolutamide on human CYP and UGT isoforms.
Based on *in vitro* CYP-induction studies in primary human hepatocytes, darolutamide might bear the risk to cause weak to moderate CYP3A4 induction in the clinic after multiple administrations in humans.	To be able to assess the actual risk of CYP3A4 induction *in vivo* after repeated darolutamide application resulting in decrease of plasma concentrations of co-administered drugs which are primarily metabolised by CYP3A4, the induction potential of darolutamide was investigated in humans (Study no. 18860).

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Studies to address the DDI potential of darolutamide towards several efflux and uptake transporters were performed *in vitro*. An inhibitory effect of darolutamide towards the efflux transporters permeability glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxic compound extrusion (MATE) 1, and MATE2K mediated transport of selected probe substrates was observed with IC_{50} values of 1.3 µM, 16.4 µM, 32.3 µM and 9.5 µM, towards BCRP, P-gp, MATE1 and MATE2K, respectively. No inhibitory effect towards the bile salt export pump (BSEP) and the multidrug resistance-associated protein 2 (MRP2) was observed.	Concomitant oral administration of darolutamide with BCRP substrates and to a lower extent with P-gp substrates, are expected to affect the respective plasma concentrations. Therefore, this was investigated in humans (studies no. 17723/BCRP and 18860/P-gp). The risk of a DDI mediated MATE transporters is considered not clinically relevant, since also with other strong MATE inhibitors (cimetidine 1.1 µM), only a limited of 27% area under the plasma concentration-time curve (AUC) increase of Metformin (MATE substrate) was observed.
An inhibitory effect of darolutamide towards the uptake transporters organic anion transporting polypeptide (OATP) 1B1, OATP1B3 and organic anion transporter (OAT) 3 was observed with IC_{50} values of 16.8 µM, 39.3 µM and 4.5 µM, after co-incubation respectively. With pre-incubation, stronger inhibition by darolutamide with IC_{50} values of 3.8 µM and 5.0 µM towards OATP1B1 and OATP1B3, respectively, was observed. No inhibitory effect towards OAT1, organic cation transporter (OCT) 1, OCT2, OATP2B1, and Na+-taurocholate cotransporting polypeptide (NTCP) was observed.	Based on the *in vitro* results, the DDI potential towards OAT3 is regarded as low; however, a clinically relevant effect by systemic inhibition of OATP1B1 and OATP1B3 cannot be ruled out. Nevertheless, the clinical relevance of inhibition of these 3 transporters was investigated in the same study as with the BCRP substrate rosuvastatin (Study no. 17723). The impact of interaction potential is described in Section 4.5 of the SmPC.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Other toxicity-related information or data	
Both, darolutamide and its metabolite keto-darolutamide absorb light in the ultraviolet (UV) range. Studies with ^{14}C-labelled darolutamide in albino and pigmented rats showed that the melanin-containing tissues, such as the pigmented skin and eyes (uveal tract/retina), contained more radioactivity than the corresponding tissues of albino rats, suggesting some binding to melanin. According to the ICH S10 guideline on photosafety evaluation, an *in vitro* 3T3 neutral red uptake phototoxicity test was conducted. The results from the *in vitro* 3T3 assay indicated that darolutamide is not phototoxic.	Darolutamide was shown to be not phototoxic on the basis of *in vitro* data.

Abbreviations: AKR = Aldo-keto reductase; AUC = Area under the plasma concentration-time curve; BCRP = Breast cancer resistance protein; BP = Blood pressure; BSEP = Bile salt export pump; CYP = Cytochrome P450; DDI = Drug-drug interaction; ECG = Electrocardiogram; FDA = Food and Drug Administration; hERG = Human ether-à-go-go-related gene; IC_{50} = Half-maximal inhibitory concentration; ICH = Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MATE = Multidrug and toxic compound extrusion; MRP2 = Multidrug resistance-associated protein 2; NTCP = Na^+-taurocholate cotransporting polypeptide; OAT = Organic anion transporter; OATP = Organic anion transporting polypeptide; OCT = Organic cation transporter; P-gp = Permeability glycoprotein; QTc = Corrected QT interval; UGT = Uridine 5'-diphospho-glucuronosyltransferase; UV = Ultraviolet.

Conclusions on Non-Clinical Data

The following list of safety concerns has been identified from non-clinical data and will be included as important identified/potential risk or missing information in Part II: Module SVII - Identified and potential risks:

Table SII.2: List of safety concerns from non-clinical data

Safety concerns	
Important identified risks (confirmed by clinical data)	None identified
Important potential risks (not refuted by clinical data or which are of unknown significance)	Carcinogenicity potential
Missing information	None identified

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The clinical development programme for darolutamide was initiated in MAR 2011. As of 07 JUN 2024, 2,394 prostate cancer patients have been treated with darolutamide in company-sponsored Phase 1–3 clinical studies worldwide (see Table SIII.1 below).

Table SIII.1 provides an overview of completed and ongoing clinical studies conducted in prostate cancer patients. All prostate cancer patients have also received ADT throughout the course of the studies (*i.e.*, luteinising hormone-releasing hormone agonist/antagonists or bilateral orchiectomy). Non-cancer subjects in the Phase 1 studies did not receive ADT.

Table SIII.1: Overview of darolutamide clinical studies in prostate cancer patients

Study no	Darolutamide dose	Main objectives	Study population	Treated patients
Phase 3 pivotal study in mHSPC – COMPLETED				
17777 ARASENS	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1,200 mg, or placebo. In combination with 6 cycles of docetaxel at 75 mg/m^2 as an IV infusion every 21 days Concurrently with ADT	Efficacy and safety compared with placebo, in combination with docetaxel	Patients with mHSPC	Darolutamide + docetaxel: 652 placebo + docetaxel: 650
Phase 3 study in mHSPC – PRIMARY COMPLETION (07 JUN 2024)				
21140 ARANOTE	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1,200 mg, or placebo Concurrently with ADT	Efficacy and safety compared with placebo	Patients with mHSPC	445 darolutamide 221 placebo
Phase 3 study in nmCRPC – COMPLETED				
17712 ARAMIS	Darolutamide 600 mg (2 tablets of 300 mg) BID	Efficacy and safety compared to placebo	Patients with nmCRPC who have	954 darolutamide 554 placebo

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Table SIII.1: Overview of darolutamide clinical studies in prostate cancer patients

Study no	Darolutamide dose	Main objectives	Study population	Treated patients
	with food, equal to a daily dose of 1,200 mg, or placebo Concurrently with ADT		undetectable metastases by conventional imaging techniques (*i.e.*, CT, MRI, BS)	170 crossed over from placebo to open-label darolutamide after study unblinding
Phase 1/2 studies in mCRPC – COMPLETED				
17829 ARADES	Phase 1: Darolutamide 100-900 mg BID; orally with food Phase 2: Darolutamide 100 mg, 200 mg, 700 mg BID. orally with food Concurrently with ADT (both phases)	Phase 1: Safety and tolerability, including DLTs and MTD, PK Phase 2: Efficacy and safety at 3 dose levels	Patients with mCRPC	134 Phase 1: 24 Phase 2: 110
18035 ARADES-EXT	Same dose as given in Week 12 of Study 17829 One dose escalation at time of disease progression was allowed	Long-term safety and tolerability, antitumour activity	Patients with mCRPC	76 patients who completed 12 weeks in Study 17829 continued to extension: from Phase 1: 19 from Phase 2: 57
17830 ARAFOR	Darolutamide 600 mg PK component: single dose orally with and w/o food Extension component: multiple dose BID orally with food Concurrently with ADT (both components).	PK Component: bioavailability, food effect: capsule and 2 different tablet formulations Extension Component: long-term safety and tolerability	Patients with mCRPC	30 15 patients per tablet formulation

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Table SIII.1: Overview of darolutamide clinical studies in prostate cancer patients

Study no	Darolutamide dose	Main objectives	Study population	Treated patients
17719	Darolutamide 300 mg (Cohort 1) 600 mg (Cohort 2) Single dose (with and w/o food) and multiple dose (with food) BID orally Concurrently with ADT	Single dose: PK and food effect Multiple dose: safety, tolerability, PK	Japanese patients with mCRPC	9 Cohort 1: 3 Cohort 2: 6
Roll-over study – ONGOING				
20321	Darolutamide at the dose and schedule specified in the feeder study Any other medication as specified in the feeder study used in combination with darolutamide	Continuation of treatment, safety	Patients receiving darolutamide in any Bayer-sponsored feeder study	676 total number of subjects (data cut-off 30 JUL 2024): 409 patients from Study 17712, 266 patients from Study 17777 and 1 patient from Study 17830
Number of prostate cancer patients exposed to darolutamide + ADT				**1,742**
Number of prostate cancer patients exposed to darolutamide + ADT + docetaxel				**652**
TOTAL number of prostate cancer patients exposed to darolutamide				**2,394**

Abbreviations: ADT = Androgen deprivation therapy; BID = Bis in die (twice daily); BS = Bone Scintigraphy; CT = Computed Tomography; DLT = Dose-limiting toxicity; IV = Intravenous; mCRPC = Metastatic castration-resistant prostate cancer; mHSPC = Metastatic hormone-sensitive prostate cancer; MRI = Magnetic Resonance Imaging; MTD = Maximum tolerated dose; nmCRPC = Non-metastatic castration-resistant prostate cancer; PK = Pharmacokinetic(s).

In addition, darolutamide was also studied in 6 completed company-sponsored clinical pharmacology studies involving 125 non-cancer subjects. As the extent and duration of exposure in non-cancer population was considerably lower than in the prostate cancer population and no relevant adverse reaction was observed in the non-cancer population, no in-detail analysis of exposure of the non-cancer population to darolutamide will be presented in

this RMP. Table SIII.2 provides an overview of completed Phase 1 studies in non-cancer subjects *i.e.*, healthy volunteers and subjects with renal or hepatic impairment.

Table SIII.2: Overview of darolutamide exposure in completed clinical studies in non-cancer subjects

Study no Report no	Dose	Main objectives	Study population	Exposed subjects
Phase 1 Single dose studies				
17721	600 mg single dose orally	PK, safety, tolerability	TOTAL Healthy volunteers Subjects with moderate hepatic impairment Subjects with severe renal impairment	29 10 9 10
17726	600 mg, 3 single doses orally	PK, safety, tolerability	Healthy volunteers	15
17831 ARIADME	Part 1: 300 mg, single oral tablet followed by single IV microtracer dose (not to exceed 100 µg) of ^{14}C-darolutamide Part 2: 300 mg single oral solution of ^{14}C-darolutamide	Bioavailability, mass balance PK, biotransformation	Healthy volunteers	12 Part 1: 6 Part 2: 6
18426	One of the following drugs administered as a single oral dose in each treatment period (Period 1–3): 300 mg darolutamide, 160 mg enzalutamide and placebo, the order of which differed between six different treatment sequence groups	Investigate drug-induced changes in grey matter CBF during single dose treatment with darolutamide or enzalutamide compared to placebo and compared to each other	Healthy volunteers	24 darolutamide

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Table SIII.2: Overview of darolutamide exposure in completed clinical studies in non-cancer subjects

Study no Report no	Dose	Main objectives	Study population	Exposed subjects
Phase 1 Multiple dose studies				
17723	Period 1: rosuvastatin alone Period 2: 600 mg single oral dose on Day 1, followed by 600 mg BID for 5 days (Days 4–8) with single dose rosuvastatin on Day 8	PK, safety	Healthy volunteers	30
18860	Period 1: DABE and MDZ alone Period 2: 600 mg oral dose BID for 11 days (with DABE on Day 3 and Day 9 and MDZ on Day 9)	PK, safety, tolerability	Healthy volunteers	15
Total	**Exposed to darolutamide**			**125**

Abbreviations: BID = bis in die (twice daily); ^{14}C = Carbon-14 (radiocarbon); CBF = Cerebral blood flow; DABE = Dabigatran etexilate; IV = Intravenous; MDZ = Midazolam; PK = Pharmacokinetics.

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SIII.1 Exposure in metastatic hormone-sensitive prostate cancer

The tables in this section present pooled data from the following studies:

Study 17777 ARASENS (n=652): Patients with mHSPC, treated with darolutamide and docetaxel

Study 21140 ARANOTE (n=445): Patients with mHSPC, treated with darolutamide and ADT

Table SIII.3: Duration of exposure (safety analyses dataset)

Duration of exposure (months)	Number of patients	Person time (years)
Up to 1 month	13	0.4
1 to <3	35	5.8
>3 to ≤6	37	13.5
>6 to ≤9	70	44.9
>9 to ≤12	62	55.3
>12 to <18	114	142.5
>18 to <24	146	259.4
≥24	620	2,140.7
Total	**1,097**	**2,662.6**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1.2/3 dated 17 JUL 2024.
Note: Total exposure for persons is given in years.
Note: For calculation, a month equals 30.44 days and a year equals 365.25 days. Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.

Table SIII.4: Duration of exposure by age group (safety analyses dataset)

Age group (years)	Number of patients	Person time (years)
18-64	360	907.0
65-74	496	1,214.3
75-84	220	507.0
≥85	21	34.3
Total	**1,097**	**2,662.6**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1.2 / 4 dated 17 JUL 2024.
Note: For calculation, a year equals 365.25 days.

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Table SIII.5: Actual dose of exposure (safety analyses dataset)

Dose of exposure	Patients	Person time (years)
300 mg qd	49	0.9
600 mg qd	395	87.8
1,200 mg qd	1,096	2,560.1
1,800 mg qd	3	0.0
Total	**1,097**	**2,648.8**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1.2 / 3 dated 17 JUL 2024.
Note: Total exposure for persons is given in years. Total includes non-dosing days. For calculation, a year equals 365.25 days. Dose refers to actual dose level, hence a subject may contribute to more than one dose level.
Abbreviations: qd = *Quaque die* (once a day).

Table SIII.6: Duration of exposure by ethnic origin (safety analyses dataset)

Race	Patients	Person time (years)
White	594	1,424.9
Black or African American	68	140.7
Asian	376	936.7
Other	16	30.0
Not reported	43	119.0
Total	**1,097**	**2,662.6**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1.2 / 5, dated 17 JUL 2024.
Note: Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 365.25 days. Race “Other” includes “American Indian or Alaska Native, “Native Hawaiian or Other Pacific Islander” and “Multiple”.

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Table SIII.7: Special populations (safety analyses dataset)

Special populations	Patients	Person time (years)
Renal function – Baseline eGFR (mL/min)		
Missing values for renal impairment	1	0.7
Normal renal function: eGFR ≥ 90 mL/min	596	1,460.1
Mild renal function impairment: 60 ≤ eGFR<90 mL/min	415	1,009.4
Moderate renal function impairment: 30 ≤ eGFR <60 mL/min	84	190.3
Severe renal function impairment: 15 ≤ eGFR < 30 mL/min	1	2.0
Hepatic function – Baseline		
Missing values for hepatic impairment	2	9.0
Normal hepatic function: Total bilirubin and AST ≤ ULN	986	2,402.1
Mild hepatic function impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin ≤ ULN and AST > ULN)	107	245.9
Moderate hepatic function impairment.: Total bilirubin > 1.5-3 x ULN, any AST	2	5.6
Total	**1,097**	**2,662.6**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1.2 / 6 dated 17 JUL 2024.

Note: Total exposure for persons is given in years. For calculation, a year equals 365.25 days. Person group allocation to special populations is based on pre-treatment assessment. eGFR was calculated according to the abbreviated MDRD formula: eGFR (mL/min/1.73m²) = k x 186 x SCR (-1.154) x age (-0.203), where k=1 for men and k=0.742 for women, SCR measured in mg/dl. The result is multiplied by 1.212 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hongkong, and Taiwan).

Abbreviations: AST = Aspartate aminotransferase; eGFR = Estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; min = Minute; mL = Millilitre, SCR = Serum creatinine; ULN = Upper limit of normal.

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SIII.2 Exposure in castration-resistant prostate cancer

The tables in this section refer to the final data for all studies.

For analysis of safety data the complete clinical trial data was analysed as follows:

Non-metastatic castration-resistant prostate cancer (nmCRPC, n=1,508) comprises data from the patients with nmCRPC at high risk for developing metastatic disease. These patients were treated with darolutamide (n=954) or placebo (n=554) in addition to androgen deprivation therapy in the double-blinded placebo-controlled Study 17712. In addition, there are 170 cross-over patients.

Metastatic castration-resistant prostate cancer (mCRPC) data pool 1 (n=173) comprises data from the patients with mCRPC, exposed to darolutamide in addition to androgen deprivation therapy in the single-arm uncontrolled Studies 17719, 17829 (incl. extension Study 18035), and 17830.

Table SIII.8: Duration of exposure (by indication)

Duration of exposure (months)	Patients	Person time (years)
Cumulative for nmCRPC and mCRPC		
≤1	24	1.0
1 to <3	75	15.2
3 to <6	77	27.8
6 to <9	92	58.6
9 to <12	78	69.2
12 to <18	121	148.4
18 to <24	105	182.6
≥24	725	2,486.3
Total	**1,297**	**2,988.9**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1 / 2 dated 10 JAN 2022.
Note: Total exposure for patients is given in years. For calculation, a month equals 30 days and a year equals 365.25 days.
Abbreviations: mCRPC = Metastatic castration-resistant prostate cancer; nmCRPC = Non-metastatic castration-resistant prostate cancer.

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Table SIII.9: Age groups of male patients (by indication)

Age group (years)	Patients	Person time (years)
Cumulative for nmCRPC and mCRPC		
18-64	189	386.4
65-74	516	1,262.2
75-84	493	1,147.0
≥85	99	193.3
Total	**1,297**	**2,988.9**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1 / 4 dated 10 JAN 2022
Note: For calculation, a month equals 30 days and a year equals 365.25 days
Abbreviations: mCRPC = Metastatic castration-resistant prostate cancer; nmCRPC = Non-metastatic castration-resistant prostate cancer.

Table SIII.10: Dose (by indication)

Dose of exposure	Patients	Person time (years)
Cumulative for nmCRPC and mCRPC		
100 mg qd	42	0.5
200 mg qd	85	18.0
300 mg qd	21	1.6
400 mg qd	52	27.9
500 mg qd	4	0.1
600 mg qd	137	55.3
700 mg qd	38	0.3
800 mg qd	1	1.4
900 mg qd	4	0.1
1,000 mg qd	3	3.2
1,200 mg qd	1,161	2,841.1
1,400 mg qd	49	28.7
1,800 mg qd	4	2.4
Total	**1,297**	**2,980.6**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1 / 3 dated 10 JAN 2022
Note: Total exposure for patients is given in years. For calculation, a month equals 30 days and a year equals 365.25 days. Dose refers to actual dose, hence a subject may contribute to more than one dose.
Abbreviations: mCRPC = Metastatic castration-resistant prostate cancer; nmCRPC = Non-metastatic castration-resistant prostate cancer; qd = *Quaque die* (once a day).

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Table SIII.11: Duration of exposure by ethnic origin (by indication)

Ethnic origin	Patients	Person time (years)
Cumulative for nmCRPC and mCRPC		
White	1,039	2,380.8
Asian	157	351.4
Black or African American	41	109.2
Hispanic or Latino	40	103.9
Not reported	7	15.4
Multiple	10	24.0
Other	3	4.2
Total	**1,297**	**2,988.9**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1 / 5 dated 10 JAN 2022
Note: Total exposure for patients is given in years. For calculation, a month equals 30 days and a year equals 365.25 days.
Abbreviations: mCRPC = Metastatic castration-resistant prostate cancer; nmCRPC = Non-metastatic castration-resistant prostate cancer.

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Table SIII.12: Special populations (by indication)

Special populations	Patients	Person time (years)
Cumulative for nmCRPC and mCRPC		
Normal renal function: eGFR ≥90 mL/min	590	1,374.9
Mild renal impairment: 60 ≤ eGFR ≤ 90 mL/min	556	1,310.1
Moderate renal impairment: 30 ≤ eGFR ≤ 60 mL/min	150	303.8
Severe renal impairment*: 15 ≤ eGFR < 30 mL/min	1	0.1
Normal hepatic function: Total bilirubin and AST ≤ ULN	1,169	2,698.6
Mild hepatic impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin ≤ULN and AST > ULN)	127	288.8
Moderate hepatic impairment: Total bilirubin >1.5 to 3 x ULN, any AST	1	1.6
Total	**1,297**	**2,988.9**

Source: BAY 1841788 Tables for Risk Management Plan, Table 1 / 6 dated 10 JAN 2022

Note: Total exposure for patients is given in years. For calculation, a month equals 30 days and a year equals 365.25 days. Person group allocation to special populations is based on pre-treatment assessment. eGFR was calculated according to the abbreviated MDRD formula: eGFR (mL/min/1.73m²) = k x 186 x SCR (-1.154) x age(-0.203), where k=1 for men and k=0.742 for women, SCR measured in mg/dl.

Note: The result is multiplied by 1.210 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hongkong, Taiwan).

*In RMP version 1.1 the category severe renal impairment was erroneously labelled as End-Stage Renal Disease.

Abbreviations: AST = Aspartate aminotransferase; eGFR = Estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; mCRPC = Metastatic castration-resistant prostate cancer; min = Minute; mL = Millilitre; nmCRPC = Non-metastatic castration-resistant prostate cancer; SCR = Serum creatinine; ULN = Upper limit of normal.

Part II: Module SIV - Populations not studied in clinical trials

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

Table SIV.1: Exclusion criteria in the pivotal studies across the development programme which are proposed/not proposed to be considered as missing information

Exclusion/inclusion criterion	Reason for exclusion	Missing information	Rationale for not including as missing information
History of metastatic disease or presence of metastatic disease at baseline.	To standardise the population with non-metastatic castration-resistant prostate cancer for analysis of primary endpoint – metastases-free survival.	No	Patients with metastatic disease are not part of the target population for the targeted marketing authorisation application.
Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer.	The comorbidity and required medical intervention introduce confounding factors that can impact some efficacy endpoints and safety analysis.	No	It is expected that the safety profile of darolutamide in these patients is similar to the studied population.
Prior treatment with second-generation AR inhibitors (such as enzalutamide, apalutamide, darolutamide, other investigational AR inhibitors) or with CYP17 enzyme inhibitors (such as abiraterone acetate, TAK-700) or oral ketoconazole longer than for 28 days.	Effects of these prior treatments on efficacy and safety endpoints could compromise the assessment of the benefits and risks of darolutamide.	No	The safety profile in these patients is not expected to be different from the profile in patients without prior exposure to AR inhibitors listed in the respective exclusion criterion.
Use of oestrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomisation and AR inhibitors (bicalutamide, flutamide, nilutamide, cyproterone acetate) at	Effects of these prior treatments on efficacy endpoints could compromise the assessment of the anti-tumour activity of darolutamide.	No	It is not expected that the safety profile of darolutamide in these patients is different.

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Table SIV.1: Exclusion criteria in the pivotal studies across the development programme which are proposed/not proposed to be considered as missing information

Exclusion/inclusion criterion	Reason for exclusion	Missing information	Rationale for not including as missing information
least 28 days before screening.			
Use of systemic corticosteroid with a dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomisation.	Due to its own anti-tumour effect systemic corticosteroids may influence efficacy endpoints and compromise the assessment of the anti-tumour activity of darolutamide.	No	It is not expected that the safety profile of darolutamide in these patients is different.
Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed >2 years before randomisation.	Standardisation of the treated population, *i.e.*, to ensure inclusion of only patients with non-metastatic castration-resistant prostate cancer.	No	It is not expected that the safety profile of darolutamide in these patients is different.
Radiation therapy (EBRT, brachytherapy, or radiopharmaceuticals) within 12 weeks before randomisation.	Standardisation of the treated population, *i.e.*, to ensure inclusion of only patients with non-metastatic castration-resistant prostate cancer.	No	It is not expected that the safety profile of darolutamide in these patients is different.
Treatment with an osteoclast targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomisation. Patients receiving osteoclast targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule	This treatment has the potential to impact the secondary efficacy endpoint - time to first skeletal event.	No	The safety profile of darolutamide in these patients is not expected to be worse than in patients not treated with osteoclast targeted therapy.

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Part II: Module SIV - Populations not studied in clinical trials

Table SIV.1: Exclusion criteria in the pivotal studies across the development programme which are proposed/not proposed to be considered as missing information

Exclusion/inclusion criterion	Reason for exclusion	Missing information	Rationale for not including as missing information
Any of the following within 6 months before randomisation: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure NYHA Class III or IV.	Due to these confounding factors the efficacy endpoint – overall survival may be impacted.	No	It is uncertain whether patients with the medical history of recent significant cardiovascular events may be at higher risk for cardiovascular disorders (progression) in association with darolutamide exposure Cardiovascular events in patients with significant CV history is considered as an important potential risk.
Prior malignancy, except for adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (*i.e.,* pTis, pTa, and pT1), as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free.	Standardisation of the treated population to minimise confounding effects of other cancer types on the efficacy endpoints related to metastasis and overall survival.	No	The safety profile of darolutamide in these patients is not expected to be different.
Gastrointestinal disorder or procedure which expects to interfere significantly with absorption of study treatment.	Due to likely reduced exposure potentially compromising assessment of effects of darolutamide.	No	Patients who cannot absorb darolutamide from the formulation as a film-coated tablet are not considered part of the target population.

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Table SIV.1: Exclusion criteria in the pivotal studies across the development programme which are proposed/not proposed to be considered as missing information

Exclusion/inclusion criterion	Reason for exclusion	Missing information	Rationale for not including as missing information
Active viral hepatitis, active HIV, Chronic liver disease, Patients with screening values of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥2.5 x upper limit of normal (ULN), total bilirubin ≥1.5 x ULN (except patients with a diagnosis of Gilbert's disease) were not eligible for inclusion in the study.	Standardisation of the treated population to reduce the impact of intrinsic (*e.g.*, affected liver metabolism, immunologic reactions) or extrinsic (drug interactions) risk factors on the efficacy endpoints and safety analysis.	No	Although darolutamide PK characteristics in patients with liver impairment were studied in dedicated clinical pharmacology trials, there is only limited clinical characterisation of darolutamide in cancer patients with moderate to severe hepatic impairment. It is uncertain whether patients with moderate to severe hepatic impairment may be at higher risk of ADRs when exposed to darolutamide in comparison to general target population. ADRs resulting from increased exposure in patients with severe hepatic impairment is considered as an important potential risk.
Renal impairment inclusion criterion for screening values of serum creatinine ≤2.0 x ULN	Standardisation of the treated population to reduce the impact of renal impairment on the efficacy endpoints and safety analysis.	Yes	Although darolutamide PK characteristics in patients with renal impairment were studied in dedicated clinical pharmacology trials, there is only limited clinical characterisation of

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Table SIV.1: Exclusion criteria in the pivotal studies across the development programme which are proposed/not proposed to be considered as missing information

Exclusion/inclusion criterion	Reason for exclusion	Missing information	Rationale for not including as missing information
			darolutamide in cancer patients with severe renal impairment. It is uncertain whether cancer patients with severe renal impairment may be at higher risk for ADRs when exposed to darolutamide in comparison to general target population
mHSPC patients with uncontrolled hypertension as indicated by a resting systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite medical management, were not eligible for inclusion in the study.	Standard exclusion criterion for clinical trials.	No	It is not known if patients with uncontrolled hypertension would be at a higher risk of ADRs. Hypertension is included as an ADR in Section 4.8 of the SmPC

Abbreviations: ADR = Adverse drug reaction; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AR = Androgen receptor; BP = Blood pressure; CV = Cardiovascular; CYP = Cytochrome P450; EBRT = External beam radiation therapy; HIV = Human immunodeficiency virus; NYHA = New York Heart Association; PK = Pharmacokinetic(s), ULN = Upper limit of normal.

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

Clinical trial development programmes are unlikely to detect rare adverse drug reactions (ADRs), due to well-known inherent limitations such as limited sample sizes, increased patient monitoring and efforts in patient education and information on the study drug and study procedures, which may already reduce the frequency of ADRs.

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

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

Type of special population	Exposure
Pregnant or breastfeeding women	Darolutamide was developed for the treatment of prostate cancer. Women are not part of the target population. No pregnant or breastfeeding women were exposed to darolutamide during the clinical development programme.
Paediatric patients below the age of 18 years	Darolutamide was developed for the treatment of prostate cancer, a disease that occurs in older men. Paediatric patients are not part of the target population. No patients below the age of 18 years were exposed to darolutamide during the clinical development phase.
Patients with renal impairment	No dose adjustment is necessary for patients with mild or moderate renal impairment. For patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily. The available data in patients with severe renal impairment are limited. As exposure might be increased those patients should be closely monitored for adverse reactions. In a clinical pharmacokinetic (PK) study, AUC and C_{max} for darolutamide were 2.5 and 1.6-fold higher in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] 15 to 29 mL/min/1.73 m^2) compared to healthy volunteers. A population PK analysis indicates a 1.1-, 1.3- and an approximately 1.5-fold higher exposure (AUC) of darolutamide in patients with mild, moderate and severe renal impairment (eGFR 15 to 89 mL/min/1.73 m^2) compared to patients with normal renal function. The PKs of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR < 15 mL/min/1.73 m^2).

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

Type of special population	Exposure
Patients with hepatic impairment	No dose adjustment is necessary for patients with mild hepatic impairment. The available data on darolutamide PKs in moderate hepatic impairment is limited. Darolutamide has not been studied in patients with severe hepatic impairment. For patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily. As exposure might be increased those patients should be closely monitored for adverse reactions. In a clinical PK study, C_{max} and AUC for darolutamide were 1.5 and 1.9-fold higher in patients with moderate hepatic impairment (Child-Pugh B) compared to healthy volunteers. There are no data for patients with severe hepatic impairment (Child-Pugh C).
Patients with severe cardiovascular impairment	Not included
Immunocompromised patients	Not included
Patients with a disease severity different from inclusion criteria in clinical trials	Not included
Population with relevant different ethnic origin	Patients of different ethnic origins, including 109 Black or African American, 533 Asian and 40 Hispanic or Latino patients were exposed to darolutamide during the clinical development.
Subpopulations carrying relevant genetic polymorphisms	No genetic polymorphism was identified as relevant during the clinical development phase.

Source: Proposed SmPC, BAY 1841788 Tables for Risk Management Plan, Table 2 / 5 dated 10 JAN 2022, BAY 1841788 Tables for Risk Management Plan, Table 1.2 / 5, dated 17 JUL 2024

Abbreviations: AUC = Area under the curve; C_{max} = Maximum observed drug concentration in measured matrix after single dose administration; eGFR = Estimated glomerular filtration rate; min = Minute; mL = Millilitre; PK(s) = Pharmacokinetic(s); SmPC = Summary of Product Characteristics.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The methodology and formula for the estimation of darolutamide patient exposure is as follows:

- Assumptions: The recommended dose is 600 mg (two film-coated tablets of 300 mg) darolutamide twice daily (BID), equivalent to a total daily dose of 1,200 mg = four tablets.
- Calculation: Number of patient years = Number of tablets sold / recommended daily dose / 365.

SV.1.2 Exposure

The estimated patient exposure to the marketed product worldwide since market approval in the US (30 JUL 2019) until 31 JAN 2024 was [redacted] patient years ([redacted] tablets sold).

Table SV.1: Nubeqa® (darolutamide) – cumulative world-wide patient exposure in total number of tablets sold and patient years 30 JUL 2019 – 31 JAN 2024

	Number of Tablets Sold Worldwide	Number of Patient Years Worldwide
Nubeqa	[redacted]	[redacted]
Total	[redacted]	[redacted]

Table SV.2: Nubeqa® (darolutamide) – cumulative sales and patient exposure per country 30 JUL 2019 – 31 JAN 2024 (EU countries)

Product	Country	Sum (Sold tablets)	Sum Exposure (Patient years)
Nubeqa, 300 mg	Austria	[redacted]	[redacted]
Nubeqa, 300 mg	Belgium	[redacted]	[redacted]
Nubeqa, 300 mg	Bulgaria	[redacted]	[redacted]
Nubeqa, 300 mg	Croatia	[redacted]	[redacted]
Nubeqa, 300 mg	Cyprus	[redacted]	[redacted]
Nubeqa, 300 mg	Czech Republic	[redacted]	[redacted]
Nubeqa, 300 mg	Denmark	[redacted]	[redacted]
Nubeqa, 300 mg	Estonia	[redacted]	[redacted]
Nubeqa, 300 mg	Finland	[redacted]	[redacted]
Nubeqa, 300 mg	France*	[redacted]	[redacted]

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Table SV.2: Nubeqa® (darolutamide) – cumulative sales and patient exposure per country 30 JUL 2019 – 31 JAN 2024 (EU countries)

Product	Country	Sum (Sold tablets)	Sum Exposure (Patient years)
Nubeqa, 300 mg	Germany	[redacted]	[redacted]
Nubeqa, 300 mg	Greece	[redacted]	[redacted]
Nubeqa, 300 mg	Hungary	[redacted]	[redacted]
Nubeqa, 300 mg	Ireland	[redacted]	[redacted]
Nubeqa, 300 mg	Italy	[redacted]	[redacted]
Nubeqa, 300 mg	Latvia	[redacted]	[redacted]
Nubeqa, 300 mg	Lithuania	[redacted]	[redacted]
Nubeqa, 300 mg	Luxembourg	[redacted]	[redacted]
Nubeqa, 300 mg	Netherlands	[redacted]	[redacted]
Nubeqa, 300 mg	Poland	[redacted]	[redacted]
Nubeqa, 300 mg	Portugal	[redacted]	[redacted]
Nubeqa, 300 mg	Romania	[redacted]	[redacted]
Nubeqa, 300 mg	Slovakia	[redacted]	[redacted]
Nubeqa, 300 mg	Slovenia	[redacted]	[redacted]
Nubeqa, 300 mg	Spain**	[redacted]	[redacted]
Nubeqa, 300 mg	Sweden	[redacted]	[redacted]
TOTAL	**EU countries**	[redacted]	[redacted]

* including French Polynesia, French Guiana, Guadeloupe, Martinique, Mayotte, New Caledonia, Reunion, Saint Pierre and Miquelon

** including Canary Islands

Not marketed in Malta

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

The pharmacological profile of darolutamide, a non-steroidal androgen receptor antagonist provided in tablet form, does not give reason to assume any risk for misuse for illegal purposes. No data on drug abuse or dependence are available. Although darolutamide inhibits 5-hydroxytryptamine, *i.e.*, serotonin uptake and γ-aminobutyric acid receptors *in vitro*, effects on the central nervous system are not expected due to the low passage of darolutamide into the brain observed in rats and mice. Controlled prescription will limit any potential risk of misuse for illegal purposes, but at present no potential for misuse or illegal use has been identified.

Part II: Module SVII - Identified and potential risks

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

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The risks listed below were identified for darolutamide during clinical development. The clinical impact of these identified risks on patients is considered to be minimal in relation to the severity of the indication treated:

- Fatigue (reflected as very common ADR, reported predominantly in severity Grade 1 or 2. Grade 3 events were reported in 0.6% of patients in the darolutamide arm and in 1.1% in the placebo arm. The event was considered serious in 1 patient in the darolutamide arm (asthenia, Grade 3). Fatigue events resulted in permanent treatment discontinuation in 0.3% and 0.2% of patients in the darolutamide and placebo arms, respectively. Events led to dose interruption in 0.3% vs. 0.7% of patients, respectively; and to dose reduction in 0.8% vs. 0.5% of patients respectively.)
- Pain in extremities (reflected as common ADR, reported in severity Grade 1 or 2. Grade 3 events were reported in 0.2% of patients in the placebo arm. There were no reports for serious events, permanent treatment discontinuation, treatment interruption or dose reduction.)
- Rash (reflected as common ADR, reported in severity Grade 1 or 2. Rash events were of worst Grade 1 or 2 in severity in all but 1 darolutamide-treated patient (0.1%), who had Grade 3 rash during the study. No serious adverse events were reported. No permanent treatment discontinuation of patients was reported for rash. Rash events led to dose interruption in 0.3% vs. 0% of patients in the darolutamide and placebo arms, respectively; and to dose reduction in 0.1% vs. 0% of patients, respectively.)
- The following laboratory parameters abnormalities were either transient or reversible after treatment discontinuation. They were not associated with any further clinically relevant abnormalities or symptoms.
  - Aspartate transaminase increased (22.5%, darolutamide vs. 13.6%, placebo arm with Grade 3-4 in 0.5% darolutamide vs. 0.2%, placebo arm);
  - Neutrophil count decreased (19.6%, darolutamide arm vs. 9.4%, placebo arm with Grade 3-4 in 3.4% darolutamide vs. 0.6%, placebo arm);
  - Bilirubin increased (16.4%, darolutamide arm vs. 6.9%, placebo arm; with Grade 3-4 in 0.1% darolutamide vs. 0%, placebo arm). The patients showed a pattern of

fluctuating bilirubin values below icteric level (3 mg/dL) with normalisation during the treatment or at the end-of-treatment visits suggesting self-limiting character of the observed hyperbilirubinaemia. Normal alkaline phosphatase and alanine aminotransferase (ALT) values as well as key contribution of indirect bilirubin to hyperbilirubinaemia indicated that the pathological changes were restricted to metabolism of bilirubin. There was no evidence for cholestatic (normal alkaline phosphatase) or hepatocellular type (normal ALT) of liver injury.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance:

The risks pertaining to this category are:

Drug-drug interactions with breast cancer resistance protein (BCRP) substrates

Darolutamide given as multiple doses of 600 mg BID to subjects in the fed state had an effect on the pharmacokinetics (PK) of the BCRP transporter substrate rosuvastatin as indicated by an approximate 5-fold increase in overall exposure and maximum plasma concentrations of rosuvastatin. The observed effect is considered to be mainly driven by inhibition of intestinal and hepatic BCRP by darolutamide and keto-darolutamide, resulting in increased rosuvastatin exposure that may be attributed to enhanced absorption and diminished biliary elimination of rosuvastatin.

Description of the DDIs with BCRP substrates is included in the Section 4.5 “Interaction with other medicinal products and other forms of interaction” of the SmPC.

Increased exposure of darolutamide in patients with severe renal impairment

Severe renal impairment led to a 1.6-fold higher peak concentration (C_{max}), a 2.5-fold higher area under the curve (AUC, 0-48), and a prolonged terminal half-life of darolutamide compared to healthy subjects. Drug exposure and maximum plasma concentration of darolutamide increased as estimated glomerular filtration rate (eGFR) decreased (negative correlation).

The results from population PK analysis (based on ARAMIS data) showed a less pronounced impact of renal impairment in nmCRPC patients compared to non-cancer subjects.

Increase of exposure in nmCRPC patients with mild or moderate renal impairment is less pronounced compared to patients with normal kidney function than the increase observed in volunteers. Therefore, in nmCRPC patients with severe renal impairment, a less than 2-fold increase of darolutamide exposure is expected (vs. patients with normal kidney function).

Based on the known observed safety profile of darolutamide from clinical trials to date, the increase of exposure was not regarded as clinically relevant.

Description of the effect of renal impairment on the exposure to darolutamide is included in the Section 4.2 “Posology and method of administration”, Section 4.4 “Special warnings and precautions for use” and in the Section 5.2 “Pharmacokinetic properties” of the SmPC.

These risks are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. It is anticipated that the respective risk minimisation messages

in the product information are adhered to by prescribers (*e.g.,* actions being part of standard clinical practice in each EU Member state where the product is authorised).

Potential risks that require no further characterisation and are followed up via routine pharmacovigilance

The following risk are associated with ADT and/or the novel anti-androgens are considered as potential risks of darolutamide due to commonality in mode of action:

- Decrease of bone mineralisation leading to osteoporosis, osteopenia and increased risk for non-metastatic bone fractures;
- Change in the body composition leading to decrease in lean body weight/sarcopenia;
- Metabolic changes predisposing to insulin resistance and dyslipidaemia;
- Increased risk for cardiovascular or cerebrovascular disorders.

The data generated in the clinical development programme for darolutamide did not provide sufficient evidence that addition of darolutamide treatment to the ADT further increases the risk for these undesirable class effects if compared to ADT alone (*i.e.,* the causal relationship between darolutamide and these potential risks is not confirmed). Furthermore, these potential risks are well known and addressed within the standard of care established for patients with prostate cancer (*e.g.,* European Association of Urology [EAU] guidelines on prostate cancer (72)). Therefore, no further characterisation or additional risk minimisation measures are deemed necessary.

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

SVII.1.2.1 Important identified risks

No important identified risks are known for Nubeqa.

SVII.1.2.2 Important Potential Risks

SVII.1.2.2.1 ADRs resulting from increased exposure in patients with severe hepatic impairment

It is uncertain whether patients with severe hepatic impairment may be at higher risk of ADRs when exposed to darolutamide in comparison to general target population.

Based on the single dose data in non-cancer patients a 1.9-fold increase in darolutamide exposure AUC (0-48) was observed in 9 subjects with moderate hepatic impairment compared to 10 healthy, age-and body weight-matched subjects (Study 17721, using Child-Pugh categorisation system for hepatic impairment).

As patients with active viral hepatitis, active human immunodeficiency virus (HIV), chronic liver disease or with screening values of serum ALT and aspartate aminotransferase (AST) ≥2.5 x upper limit of normal (ULN), total bilirubin ≥1.5 x ULN (except patients with a diagnosis of Gilbert's disease) were not eligible for inclusion in the pivotal Phase 3

Study 17712 (ARAMIS). Clinical data in patients with severe hepatic impairment is not available.

No clinically relevant impact on darolutamide exposure is expected when nmCRPC patients with severe hepatic impairment (categorised either by the Child-Pugh system or the National Cancer Institute Organ Dysfunction Working Group [NCI-ODWG] criteria) receive the recommended dose of 600 mg darolutamide BID. There is no evidence that the safety profile of darolutamide in patients with severe hepatic impairment is expected to be different from that in the general target population.

A post-hoc analysis was conducted to explore a potential relationship between the incidence rate of ADRs and the exposure [AUC(0 12)] of darolutamide in the patients of Study 17712. The exposure data were not only calculated for the 388 patients of the PK subgroup but also for all remaining patients based on the updated Phase 3 population PK model. The analysis of ADRs (grouped term ‘fatigue/asthenic conditions’; grouped term ‘rash’ and Preferred Term [PT] pain in extremity) did not reveal a correlation between the incidence of ADRs and the exposure [AUC(0 12)] of darolutamide. The overall incidence of treatment-emergent adverse events (TEAEs) considered as ADRs for darolutamide was similar among the different exposure quartiles – 20.1%, 21.4%, 25.2% and 22.2% for exposure quartiles 1, 2, 3 and 4, respectively. The exposure quartiles covered an AUC(0-12) range from 14.0 to 127 h·mg/L. The incidence of ADRs by worst grade was also similar between the different exposure quartile subgroups.

Routine pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by risk minimisation measures such that the benefit-risk for the product is positive. In addition, adverse event (AE) follow-up questionnaires are implemented in cases of ADRs reported in patients with history of hepatic impairment treated with Nubeqa.

SVII.1.2.2.2 Cardiovascular events in patients with significant CV history

As the patients with recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV were excluded from the pivotal clinical Study 17712, there is only limited clinical characterisation of darolutamide in patient population.

The ADT-associated changes in body composition, lipids, and insulin sensitivity are suspected to increase the risk for diabetes and cardiovascular disorders in prostate cancer patients.

Analysis of safety data from clinical Study 17712, including subgroup analysis of patients with medical history of cardiovascular disorders, did not reveal any meaningful imbalance between the treatment arms suggesting that darolutamide may increase the risk of cardiovascular events when added to ADT.

It is uncertain whether patients with the medical history of recent significant cardiovascular events may be at higher risk for cardiovascular disorders (progression) in association with darolutamide exposure.

Routine pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by risk minimisation measures such that the benefit-risk for the product is positive. In addition, AE follow-up questionnaires are implemented in cases of cardiac disorder in patients treated with Nubeqa.

SVII.1.2.3 Missing information

SVII.1.2.3.1 Use in patients with severe renal impairment

As patients with serum creatinine (SCR) ≥2.0 x ULN at screening visit were not eligible for inclusion in the pivotal Phase 3 Study 17712 (ARAMIS), there is only limited clinical characterisation of darolutamide in cancer patients with severe renal impairment.

A 1.5- to 2.5-fold increase in AUC of darolutamide exposure may be expected in nmCRPC patients with severe renal impairment. It is uncertain whether patients with severe renal impairment may be at higher risk for ADRs when exposed to darolutamide in comparison to general target population. In addition, AE follow-up questionnaires are implemented in cases of ADRs reported in patients with history of renal impairment treated with Nubeqa.

SVII.1.2.3.2 Carcinogenicity potential

No carcinogenicity studies were conducted in accordance with the recommendations in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guideline since the proposed indication is for advanced cancer. Furthermore, the results of chronic repeat-dose toxicity studies in male and female rats and dogs at multiples up to 4 to 5-fold the therapeutic exposure did not show signs of off-target toxicity or proliferative tissue lesions indicative of a risk of secondary neoplasias following prolonged treatment with darolutamide. Also, darolutamide did not show relevant genotoxicity in a standard package of *in vitro* and *in vivo* studies. Therefore, further animal studies for the assessment of a potential carcinogenicity of darolutamide were not originally considered warranted.

In order to further assess the carcinogenic potential of darolutamide, additional pharmacovigilance activities are proposed in non-clinical species. The proposed Category 3 study (A study to assess the carcinogenic potential in mice) will evaluate the effects of daily oral administration of darolutamide for a period of 6 months in tg-rasH2 transgenic mouse model.

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

Not applicable.

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Part II: Module SVII - Identified and potential risks

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

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important potential risk: ADRs resulting from increased exposure in patients with severe hepatic impairment

Potential mechanisms:

Increase in darolutamide exposure in patients with severe hepatic impairment.

Evidence source(s) and strength of evidence:

It is uncertain whether patients with severe hepatic impairment may be at higher risk of ADRs when exposed to darolutamide in comparison to general target population.

Patients with active viral hepatitis, active HIV, chronic liver disease or with screening values of serum ALT and AST ≥2.5 x ULN, total bilirubin ≥1.5 x ULN (except patients with a diagnosis of Gilbert's disease) were not eligible for inclusion in the pivotal Phase 3 Studies 17712 (ARAMIS) and 17777 (ARASENS).

Based on the single dose data in non-cancer patients a 1.9-fold increase in darolutamide exposure $AUC_{(0-48)}$ was observed in 9 subjects with moderate hepatic impairment compared to 10 healthy, age- and body weight-matched subjects (Study 17721, using Child-Pugh categorisation system for hepatic impairment).

Characterisation of the risk

Clinical trials

Phase 3 Study 17712 (ARAMIS):

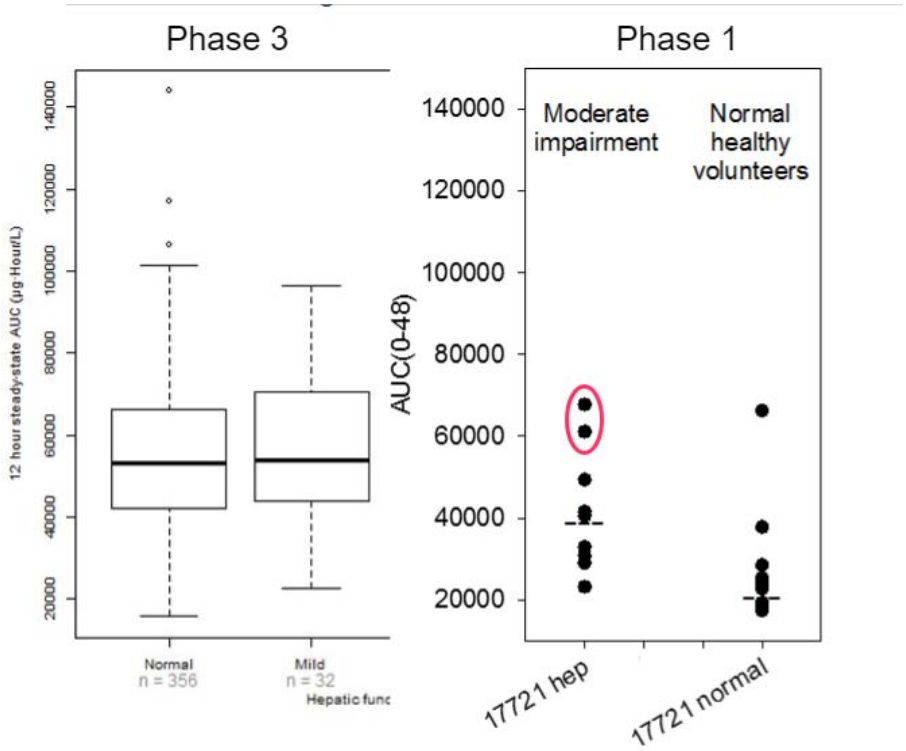
As patients with active viral hepatitis, active HIV, chronic liver disease or with screening values of serum ALT and AST ≥2.5 x ULN, total bilirubin ≥1.5 x ULN (except patients with a diagnosis of Gilbert's disease) were not eligible for inclusion in the pivotal Phase 3 Study 17712 (ARAMIS), there were no patients with severe hepatic impairment in nmCRPC pool. Overall, based on NCI-ODWG criteria the number of patients with moderately impaired hepatic function was low and comparable between the treatment arms (n=2 in darolutamide and n=1 in placebo arm) in the Study 17712. In the mCRPC pool, there was no patients with moderate or severe hepatic impairment.

The population PK analysis of the data from the Phase 3 Study 17712 suggests that the impact of hepatic impairment was distinctly less pronounced in the nmCRPC patients. Overall, based on NCI-ODWG criteria 89 patients with mild and 2 patients with moderate hepatic impairment who received darolutamide treatment were included in the analysis. The population PK analysis of Study 17712 did not identify hepatic impairment as a significant covariate for darolutamide exposure in the target population with intended use of darolutamide (*i.e.*, in multiple dose regimen). Due to lack of significant effect of hepatic impairment on darolutamide exposure and the overall low number of patients, no evaluation

of patients with severe hepatic and co-existent renal impairment was feasible in the population PK analysis of Study 17712.

The exposure in the 2 non-cancer subjects from Study 17721 categorised by NCI-ODWG as mild or moderate hepatic impairment was in the same range as the exposure in nmCRPC patients with mild hepatic impairment (see Figure SVII.1).

Figure SVII.1: Comparison of steady-state $AUC_{(0\text{-}12)ss}$ in nmCRPC patients stratified by hepatic function according to NCI criteria from Study 17712 and single dose $AUC_{(0\text{-}48)}$ in male volunteers stratified by hepatic function according to Child-Pugh criteria (NCI categorisation is additionally provided) for Study 17721



Abbreviations: AUC(0-48) = area under the plasma concentration time curve from 0 to 48 hours post dose; NCI = National Cancer Institute; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group; nmCRPC = non-metastatic castration-resistant prostate cancer.
Red circles indicate 2 subjects with mild or moderate hepatic impairment according to NCI-ODWG.

Analysis of safety variables revealed no meaningful differences between the hepatic function groups or treatment arms in the overall incidence of TEAEs, or in the incidence of TEAEs with worst grade of 3, 4 or 5.

An additional analysis to explore a potential relationship between the incidence rate of ADRs and the exposure [$AUC_{(0\text{-}12)ss}$] of darolutamide in the patients of Study 17712 did not reveal any meaningful correlation (*i.e.*, incidence of ADRs [including fatigue/asthenic conditions; rash and pain in extremity] by worst grade was similar between the different exposure quartile

subgroups). Additionally, there appears no relationship between darolutamide exposure and increase of serum bilirubin in patients participating in Study 17712.

Based on the single dose data in non-cancer patients a 1.9-fold increase in darolutamide exposure $AUC_{(0-48)}$ was observed in 9 subjects with moderate hepatic impairment compared to 10 healthy, age- and body weight-matched subjects (Study 17721, using Child-Pugh categorisation system for hepatic impairment). Patients with severe hepatic impairment were not studied. Due to co-existing renal impairment in some subjects with moderate hepatic impairment in Study 17721 the effect on exposure to darolutamide and its metabolites was partly driven by renal impairment only.

Phase 3 Study 17777 (ARASENS):

Based on the laboratory values at baseline, there were only 2 mHSPC patients with moderate hepatic impairment in Study 17777. In the two patients with moderate hepatic impairment, $AUC_{(0–12)ss}$ was lower (16% lower in one patient, and 3% lower in the other patient) compared with patients with normal hepatic function.

The review of medical history identified patients with any of the following Medical Dictionary for Regulatory Activities (MedDRA) PTs potentially relevant to hepatic impairment:

Alcoholic liver disease, Cirrhosis alcoholic, Drug-induced liver injury, Endoscopic retrograde cholangiopancreatography, Haemangioma of liver, Hepatic cirrhosis, Hepatic function abnormal, Hepatic steatosis, Hepatitis, Hepatitis alcoholic, Hepatobiliary disease, Hepatomegaly, Liver abscess, Liver disorder, Liver transplant, Steatohepatitis.

In the darolutamide + docetaxel arm, there were 18 patients with medical history potentially relevant to hepatic impairment and 634 patients without history of hepatic impairment. In the placebo + docetaxel arm, there were 19 patients with medical history potentially relevant to history of hepatic impairment and 631 patients without history of hepatic impairment.

The 18 patients in the darolutamide + docetaxel arm presented the following medical history PTs: Hepatic steatosis (N=7), Hepatic cirrhosis (N=2), Hepatitis, Hepatic function abnormal, Alcoholic liver disease, Hepatitis alcoholic, Liver abscess, Hepatomegaly, Haemangioma of liver, Hepatobiliary disease, and Liver disorder.

Most of them (11) did not report a serious adverse event (SAE). In 7 of them, the following SAEs were reported: Ischaemic heart disease (Grade 1), Febrile Neutropenia (Grade 4) and Neutropenic Sepsis (Grade 4), Pain in Metastases Prostate Carcinoma (Grade 3), Encrustation of Ureteric Stent (Grade 2), Reflux Esophagitis (Grade 2), ALT Increased (Grade 1), Left Atrial Appendage Occlusion (Grade 3).

Febrile Neutropenia (Grade 4) and Neutropenic Sepsis (Grade 4) reported in one subject were considered related to docetaxel by the investigator; the events led to interruption of darolutamide and docetaxel and the events resolved.

Pain in Metastases Prostate Carcinoma (Grade 3) led to darolutamide discontinuation.

Darolutamide dose was not changed in the remaining 5 of the 7 patients.

Overall, no distinctive patterns were noted in the incidence of TEAEs between the darolutamide + docetaxel and placebo + docetaxel arms. The review of SAEs in subjects with medical history of hepatic impairment did not reveal any specific risk associated to the treatment with darolutamide in combination with docetaxel.

Phase 3 Study 21140 (ARANOTE):

Based on the laboratory values at baseline, there were no mHSPC patients with moderate or severe hepatic impairment in Study 21140. The number of participants with mild impairment of hepatic function at baseline was N=58 and N=19 in the darolutamide and placebo arms, respectively.

The review of medical history identified patients with any of the following MedDRA PTs potentially relevant to hepatic impairment:

Alcoholic liver disease, Cirrhosis alcoholic, Drug-induced liver injury, Endoscopic retrograde cholangiopancreatography, Haemangioma of liver, Hepatic cirrhosis, Hepatic function abnormal, Hepatic steatosis, Hepatitis, Hepatitis alcoholic, Hepatobiliary disease, Hepatomegaly, Liver abscess, Liver disorder, Liver transplant, Steatohepatitis.

In the darolutamide arm, there were 17 patients with medical history potentially relevant to hepatic impairment and 428 patients without history of hepatic impairment. In the placebo arm, there were 6 patients with medical history potentially relevant to history of hepatic impairment and 215 patients without history of hepatic impairment.

A review of AEs in subjects with a medical history of hepatic impairment in the darolutamide arm did not reveal evidence of an increased risk for hepatic function-related undesirable effects with darolutamide treatment.

Post-marketing data excluding pivotal trials (ARAMIS, ARASENS and ARANOTE):

Retrieval criteria

A cumulative search of Bayer's Global Safety Database was performed for reports of patients with medical history coded to any of the following MedDRA High Level Term (HLT) Hepatic failure and associated disorders, HLT Hepatocellular damage and hepatitis NEC, HLT Hepatic enzymes and function abnormalities, and HLT: Liver function analyses (decreased, increased, abnormal in PT terms).

Case presentation

The search strategy yielded 67 cases that met the above search criteria, received *cumulatively* from post-marketing sources since market launch (30 JUL 2019) up to 30 JAN 2024.

In the 67 patients with relevant medical history of hepatic impairment, a total of 196 events (55 serious and 141 non-serious events) were reported. Table SVII.1 presents an overview of all events by PT which were reported with a frequency of ≥2 events.

The PT reported with the highest frequency (14 events per PT) was Fatigue. Further, events with a frequency of n=7 were reported for Hepatic function abnormal, with a frequency of

n=6 were reported for Alanine aminotransferase increased, Arthralgia, and with a frequency of n=5 were reported for Off label use.

Table SVII.1: Preferred Terms reported more than once in patients with a medical history of hepatic impairment

Preferred Term	Non-serious AEs[1]	Serious AEs[1]	Total AEs[1]
All AEs	**141[1]**	**55[1]**	**196[1]**
Fatigue	12	2	14
Hepatic function abnormal	5	2	7
Alanine aminotransferase increased	6	-	6
Arthralgia	6	-	6
Off label use	5	-	5
Aspartate aminotransferase increased	4	-	4
Dizziness	3	1	4
Headache	3	1	4
Insomnia	4	-	4
Product dose omission issue	4	-	4
Asthenia	2	1	3
Diarrhoea	3	-	3
Hot flush	3	-	3
Malaise	2	1	3
Nausea	3	-	3
Pain in extremity	2	1	3
Rash	3	-	3
Somnolence	2	1	3
Blood alkaline phosphatase increased	-	2	2
Blood bilirubin increased	2	-	2
Decreased appetite	2	-	2
Drug-induced liver injury	1	1	2
Fall	1	1	2
Hormone-refractory prostate cancer	-	2	2
Hyponatraemia	1	1	2
Liposarcoma	2	-	2
Liver disorder	2	-	2
Nasopharyngitis	2	-	2
Oedema peripheral	1	1	2

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Table SVII.1: Preferred Terms reported more than once in patients with a medical history of hepatic impairment

Preferred Term	Non-serious AEs[1]	Serious AEs[1]	Total AEs[1]
Pollakiuria	2	-	2
Prostatic specific antigen increased	2	-	2

[1]Note that the numbers of events for the individual PTs do not add up to the overall number of "all AEs", as not all events are shown. Only those PTs that were reported with a frequency of ≥2 events are shown.
Abbreviations: AE = Adverse event, PT = Preferred Term.

The review of the five non-serious reports of Off-label use revealed that 3 out of 5 patients started on 600 mg darolutamide per day, which is consistent with the label recommendations for patients with moderate hepatic impairment. In the remaining two patients, darolutamide was used in an unapproved indication (mCRPC and mHSPC) at the time of the report.

Overall, four cases in total reported a fatal outcome or death. In three cases ([redacted], [redacted], [redacted]) the patients died due to progression of the underlying prostate cancer. In one case ([redacted]) a subject with preexisting hepatitis C and ascites died 4 months after the last dose of darolutamide due to liver failure, which likely reflects the natural progression of the hepatic disease.

Conclusion

The review of the AEs reported in patients with medical history of potentially severe hepatic impairment did not identify any particular risks associated with darolutamide.

Risk factors and risk groups:

Patients with severely impaired hepatic function.

Preventability:

Close monitoring of patients with impaired hepatic function. Darolutamide dose reduction in patients with moderate and severe hepatic impairment.

For patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily.

Impact on the risk-benefit balance of the product:

No clinically relevant impact on darolutamide exposure is expected when mHSPC and nmCRPC patients with moderate and severe hepatic impairment (categorised either by the Child-Pugh system or the NCI-ODWG criteria) receive the recommended reduced dose of 300 mg darolutamide BID. There is no evidence to date that the safety profile of darolutamide in patients with severe hepatic impairment is expected to be different from that in the general target population.

Routine pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact:

The public health impact is expected to be low.

SVII.3.1.2 Important potential risk: Cardiovascular events in patients with significant CV history

Potential mechanisms

Increase in frequency of TEAEs in patients with significant cardiovascular history.

Evidence sources and strength of evidence

The ADT-associated changes in body composition, lipids, and insulin sensitivity are suspected to increase the risk for diabetes and cardiovascular disorders in prostate cancer patients. The overall evidence is, however, conflicting and the relationship between ADT and cardiovascular disorders remains unclear (73).

Patients with recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; and congestive heart failure NYHA Class III or IV were excluded from the pivotal clinical Studies 17712 (ARAMIS) and 17777 (ARASENS).

It is uncertain whether patients with the medical history of recent significant cardiovascular events may be at higher risk for cardiovascular disorders (progression) in association with darolutamide exposure.

Characterisation of the risk

Clinical trials

To reduce the impact on the efficacy endpoints (*e.g.*, overall survival) the patients with confounding risk factors for increased mortality *i.e.,* with recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure NYHA Class III or IV were excluded from the pivotal clinical Studies 17712, 17777, and 21140.

Phase 3 Study 17712 (ARAMIS)

Analysis of safety data from clinical Study 17712, including subgroup analysis of patients with medical history of cardiovascular disorders, did not reveal any meaningful imbalance between the treatment arms suggesting that darolutamide may increase the risk of cardiovascular events when added to ADT.

In Study 17712 (SAF), the QTcB and QTcF values were similar between the darolutamide and placebo arms at baseline. Overall, there were no notable treatment arm differences with respect to the proportion of patients with changes in QTc from baseline or the proportion of patients with QTc interval prolongation.

The analysis of the electrocardiogram (ECG) abnormalities in the cardiac electrical conduction system, ectopic activity, cardiac rhythm and ST segment did not reveal any relevant imbalance between the treatment arms nor changes from baseline.

In the mCRPC pool, no notable changes from baseline were seen in any of the ECG parameters and no dose dependent increases in PR or QTc intervals were observed in these studies.

A dedicated analysis of the potential effect of darolutamide on cardiac repolarisation was performed in a PK subset of the Phase 3 Study 17712 (ARAMIS). These patients had baseline ECGs and at least one triplicate ECG collection during darolutamide/placebo treatment, time matched to a PK sample. The PK samples covered the entire PK profile of darolutamide, including C_{max}. The primary objective of this analysis was a concentration-QTc modelling approach assessing the effect of darolutamide on cardiac repolarisation. As secondary objectives, central tendency analyses were performed using the endpoint "change from baseline" at different times post-drug administration and different times post-start of study drug treatment, *i.e.,* different visits. Primary and secondary objectives were investigated in slightly different subsets. The concentration-QTc effect was analysed in 323 patients receiving darolutamide and in 177 patients receiving placebo. The central tendency analysis was performed in 337 and 183 patients, respectively. As there was no evidence that darolutamide exposure has an effect on heart rate the final assessment on cardiac repolarisation focused on QTcF for all analyses. The QTc substudy and the ECG results from the total safety population of Study 17712 demonstrated that darolutamide had no clinically relevant effects on heart rate, PR and QRS interval duration or interval, nor any clinically significant effect on cardiac repolarisation (QTc). The concentration-QTc relationship showed a negative slope and the upper limit of 95% one-sided CI of the ΔΔQTcF value did not exceed 10 ms.

Phase 3 Study 17777 (ARASENS)

For the analysis of the topic cardiac disorders, the pre-defined grouped term "cardiac disorders" included High Level Group Terms (HLGTs) cardiac arrhythmias, coronary artery disorders and heart failures. These HLGTs were selected for the analysis due to treatment arm differences observed in the incidences of TEAEs within these HLGTs in the prior Phase 3 Study 17712 of darolutamide in nmCRPC.

In ARASENS study, the TEAEs within the grouped term "cardiac disorders" were reported with a comparable incidence (10.9% vs. 11.7%) in the darolutamide + docetaxel arm and in the placebo + docetaxel arm, respectively. The events were considered as Treatment-emergent serious adverse events (TESAEs) in 2.9% of patients in both treatment arms. Similar to the grouped term of cardiac disorders, the overall incidence (12.7% vs. 13.8%) of TEAEs within the System Organ Class (SOC) cardiac disorders was similar in the darolutamide + docetaxel arm and in the placebo + docetaxel arm, respectively. The events were mostly reported with Grade 1 or 2 as the worst grade in both treatment arms.

The incidences of TEAEs of cardiac disorders were reviewed by medical history of cardiac disorders (SOC). Altogether, 112 patients in the darolutamide + docetaxel arm and

128 patients in the placebo + docetaxel arm had a medical history of cardiac disorders before the start of study treatment. In both treatment arms, the incidence of TEAEs within the SOC cardiac disorders was higher in patients who had a history of cardiac disorders, and this difference was more evident in patients in the placebo + docetaxel arm.

A summary of TEAEs reported within the HLGTs cardiac arrhythmias, coronary artery disorders and heart failures is provided below.

Cardiac arrhythmias:

TEAEs within the HLGT cardiac arrhythmias were reported with a similar incidence (8.0% vs. 8.5%) in the darolutamide + docetaxel arm and the placebo + docetaxel arm, respectively. The majority of the events were reported with a worst grade of 1 or 2. An analysis of the ECG data over time (by visit) did not reveal any relevant imbalance between the treatment arms nor changes from baseline. Fridericia QTc results were in general similar between treatments arms, and within a treatment arm, at baseline, end of treatment, and last visit. Baseline ECG abnormalities were observed at a similar incidence in patients in the darolutamide + docetaxel arm and the placebo + docetaxel arm. TEAE electrocardiogram QT prolonged was reported in 5 patients (0.8%) in the darolutamide + docetaxel arm and in 7 patients (1.1%) in the placebo + docetaxel arm. All these were reported as non-serious events and the study drug doses were not modified due to the events in any of the patients.

In conclusion, the review of the cardiac arrhythmias as well as the ECG data over time did not suggest any relevant pro-arrhythmic effect of darolutamide when used in combination with docetaxel.

Coronary artery disorders:

TEAEs within the HLGT coronary artery disorders were reported with a small difference between the darolutamide + docetaxel arm and the placebo + docetaxel arm (2.9% vs. 2.0%, respectively). When adjusted for the difference in study drug treatment duration, the exposure-adjusted incidence rate (EAIR) was 1.1 per 100 PY in both treatment arms.

Two fatal events of myocardial infarction were reported in the darolutamide + docetaxel arm. In both treatment arms, coronary artery disorders were more commonly reported in patients who had a medical history of cardiac disorders. With the known history of patients who experienced cardiac disorders along with the known side effects of ADT causing metabolic changes contributing to these events, no evidence was seen to link the events to darolutamide.

Heart failure:

TEAEs within the HLGT heart failures were reported in 0.6% vs. 2.0% of patients in the darolutamide + docetaxel arm and the placebo + docetaxel arm, respectively. Darolutamide was not found to increase the risk of heart failure in comparison with placebo, both in combination with docetaxel and ADT.

Phase 3 Study 21140 (ARANOTE):

The analysis of safety data from clinical Study 21140, including subgroup analysis of patients with medical history of cardiovascular disorders, did not reveal any meaningful imbalance

between the treatment arms suggesting that darolutamide may increase the risk of cardiovascular events when added to ADT.

In the darolutamide arm of the ARANOTE study, the incidence of cardiac disorder TEAEs was higher in the presence of a medical history of cardiac disorders (20.7% vs. 11.3%). This was also observed in the placebo arm, where the incidence of cardiac disorder TEAEs was higher in the presence of a medical history of cardiac disorders (11.9% vs. 8.4%).

A summary of TEAEs reported within the HLGTs cardiac arrhythmias, coronary artery disorders and heart failures is provided below.

Cardiac arrhythmias:

The overall incidence of cardiac arrhythmia TEAEs in the darolutamide arm was higher in the presence of a medical history of cardiac disorders (10.9% vs. 8.2%). This was also observed in the placebo arm, where the incidence of cardiac arrhythmia TEAEs was higher in the presence of a medical history of cardiac disorders (7.1% vs. 6.7%).

Coronary artery disorders:

The overall incidence of coronary artery disorder TEAEs in the darolutamide arm was higher in the presence of a medical history of cardiac disorders (6.5% vs. 2.8%). This was also observed in the placebo arm, where the incidence of coronary artery disorder TEAEs was higher in the presence of a medical history of cardiac disorders (2.4% vs. 1.1%).

Heart failures:

The overall incidence of heart failure TEAEs in the darolutamide arm was higher in the presence of a medical history of cardiac disorders (2.2% vs. 0.6%). This was also observed in the placebo arm, where the incidence of heart failure TEAEs was higher in the presence of a medical history of cardiac disorders (2.4% vs. 0.6%).

Conclusion:

In both treatment arms, participants with a medical history of cardiac disorder experienced cardiac related TEAEs at a higher incidence than those without such medical history. This suggests that darolutamide did not increase the risk of developing a cardiac event in comparison with placebo. This conclusion was further supported by the ARANOTE + ARAMIS pooled analysis.

Post-marketing data excluding pivotal trials (ARAMIS, ARASENS and ARANOTE)*:*

Retrieval criteria

A search of Bayer's Global Safety Database was performed for the AEs coded to any of the MedDRA HLGTs Cardiac arrhythmias, Coronary artery disorders and Heart Failure in patients with medical history coded to any of the HLGTs Coronary artery disorders, Cardiac arrhythmias and Heart Failure and PTs: Coronary artery bypass, Percutaneous coronary intervention, Coronary revascularisation.

Case presentation

The search yielded 112 cases with cardiac related events in patients with significant CV medical history received *cumulatively* from all sources since market launch (30 JUL 2019) up to 30 JAN 2024.

Table SVII.2 below presents a list of PTs of relevant significant cardiovascular medical history (≥5 events per PT). Most common PTs were Atrial fibrillation (n=32), Coronary artery disease (n=18), and Myocardial infarction (18).

Table SVII.2: Relevant medical history in patients with significant cardiovascular history1 by MedDRA Preferred Term. Please note that only PTs with ≥5 events are presented.

Preferred Term	Number of events*
Atrial fibrillation	32
Coronary artery disease	18
Myocardial infarction	18
Cardiac failure congestive	12
Peripheral swelling	12
Cardiac failure	11
Myocardial ischaemia	8
Angina pectoris	7
Coronary artery bypass	7
Arrhythmia	5

[1] MedDRA HLGTs Cardiac arrhythmias, Coronary artery disorders and Heart Failure and medical history coded to HLGTs Coronary artery disorders, Cardiac arrhythmias and Heart Failure and PTs: Coronary artery bypass, Percutaneous coronary intervention, Coronary revascularisation.

* Please note that only PTs with ≥5 events are presented

Abbreviations: HGLT = High Level Group Term; MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term.

Table SVII.3 below summarizes a list of all PTs of AEs that met the search criteria. The most commonly reported cardiovascular AEs were Peripheral swelling (total 25 events; 22 non-serious and 3 serious events), Atrial fibrillation (16 serious events), Chest pain (total 12 events; 5 non-serious events and 7 serious events), Oedema peripheral (total 12 events; 10 non-serious and 2 serious events), Cardiac failure congestive (10 serious events).

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Table SVII.3: Tabulation by Preferred Term for all relevant cardiovascular adverse events reported in patients with significant cardiovascular history that met retrieval criteria reported cumulatively from all sources since market launch (30 JUL 2019) up to 30 JAN 2024, excluding pivotal trials

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
All AEs	**48**	**90**	**138**
Peripheral swelling	22	3	25
Atrial fibrillation	0	16	16
Chest pain	5	7	12
Oedema peripheral	10	2	12
Cardiac failure congestive	0	10	10
Angina pectoris	1	8	9
Cardiac failure	0	8	8
Myocardial infarction	0	7	7
Chest discomfort	5	1	6
Acute coronary syndrome	0	5	5
Arrhythmia	2	2	4
Myocardial ischaemia	0	2	2
Acute myocardial infarction	0	2	2
Bradycardia	0	2	2
Coronary artery disease	0	2	2
Cardiac failure acute	0	2	2
Cardiac flutter	0	2	2
Pulseless electrical activity	0	1	1
Torsade de pointes	0	1	1
Supraventricular tachycardia	0	1	1
Atrial flutter	0	1	1
Cardiac arrest	0	1	1
Hypervolaemia	1		1
Sudden death	0	1	1
Atrioventricular block second degree	0	1	1
Tachycardia	1		1
Ascites	1		1
Acute left ventricular failure	0	1	1
Cardio-respiratory arrest	0	1	1

Abbreviations: AE = Adverse event.

One spontaneous case was reported in an [redacted] male patient who received darolutamide for CRPC and experienced a SAE of Torsade de pointes. The patient's medical history included the following PTs: Ventricular fibrillation, Sinus rhythm and Ventricular extrasystoles. Concurrent conditions included Myasthenia gravis, Myelodysplastic syndrome, Cardiac failure chronic, Aortic valve stenosis (After Transcatheter aortic valve implantation), Bronchial asthma and Hypertension. From 26 MAY 2021 until 01 JUN 2021, patient received darolutamide. On 01 JUN 2021, the patient experienced Torsade de pointes (seriousness criterion life threatening) with Chest discomfort. darolutamide was withdrawn. The event was assessed as unrelated to darolutamide. The reporter considered the medical history as specified above to provide plausible alternative explanations for the development of the Torsade de pointes.

Nine fatal cardiac events were reported of the total 112 cases (two events of Acute coronary syndrome, and one event of each: Aortic rupture, Myocardial infarction, Myocardial ischaemia, Cardiac arrest, Cardiac failure congestive, Sudden death and Cardio-respiratory arrest).

Conclusion

Based on the review of the cumulative data, no safety concern was identified for darolutamide in the subgroup of patients with medical history of cardiovascular disorders.

Risk factors and risk groups

Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and congestive heart failure NYHA Class III or IV were excluded from the pivotal studies.

Preventability

Patients should be treated for these conditions according to established treatment guidelines.

Impact on the risk-benefit balance of the product

Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact

At present public health impact is unknown and expected to be low, as patients with significant cardiovascular history were not included in pivotal trials.

SVII.3.1.3 Important potential risk: Carcinogenicity potential

Potential mechanisms:

The potential mechanism for the observed second primary malignancies (SPMs) in humans treated with darolutamide is unknown. The most common types of tumours reported in clinical trials and in the post-marketing setting do not suggest any relationship to antiandrogenic effects.

Evidence source:

In the pivotal Phase 3 clinical trials ARAMIS (Study 17712) and ARASENS (Study 17777), a slight numerical imbalance was only observed in the incidence of all SPM in Study 17777 in the darolutamide + docetaxel arm compared to the placebo + docetaxel arm (3.8% vs. 2.5%, respectively) (Table SVII.6). However, after adjusting for study treatment duration, the EAIR per 100 PY was similar between treatment arms (1.4 and 1.3 in the darolutamide + docetaxel arm and placebo + docetaxel arm, respectively). The relative risk (RR) of SPM for patients treated in the darolutamide + docetaxel vs. placebo + docetaxel arm was 1.56 (95% CI: [0.84; 2.89]). After excluding superficial skin cancers, the incidences of SPM were similar in the darolutamide + docetaxel arm and the placebo + docetaxel arm (2.9% vs. 2.0%, respectively), with the same EAIR in both treatment arms (1.1 per 100 PY) (Table SVII.7).

Nonclinical safety data of darolutamide do not indicate a carcinogenic potential. The results of chronic repeat-dose toxicity studies in male and female rats and dogs at multiples up to 4 to 5-fold the therapeutic exposure did not show signs of off-target toxicity or proliferative tissue lesions indicative of a risk of secondary neoplasia following prolonged treatment with darolutamide. Also, darolutamide did not show relevant genotoxicity in a standard package of *in vitro* and *in vivo* studies. In addition, in the pivotal 26-week carcinogenicity study with orally administered darolutamide in 001178-T (hemizygous) RasH2 mice, no darolutamide-related effects were noted on the incidence or type of neoplasms. At the maximum feasible dose of 1,000 mg/kg/day, exposure was 0.9 - 1.3 times the clinical exposure in humans at the therapeutic dose of 600 mg BID. In conclusion, no carcinogenic potential was observed up to the highest darolutamide dose administered in the carcinogenicity study. Taking into account the darolutamide exposure in this study within the range of clinical exposure, this study may not fully exclude the potential risk of carcinogenicity.

In 2-year carcinogenicity studies in rats with other second-generation androgen receptor inhibitor drugs in the same pharmacological class as darolutamide, neoplastic findings of unknown relevance to humans were observed.

Characterisation of the risk:

Clinical trial data:

Phase 3 Study 17712 (ARAMIS):

A summary of the incidence of SPM AEs during the treatment and in follow-up period is presented in Table SVII.4 below.

The incidence of SPM AEs was similar between the treatment arms (2.8% in the darolutamide arm and 2.9% in the placebo arm). Out of the 27 patients with SPM AEs in the darolutamide arm, the most frequently reported PTs (≥2) were basal cell carcinoma (n=5), colon cancer, pancreatic carcinoma (both n=3 each), malignant melanoma in situ, rectal adenocarcinoma, rectal cancer (all n= 2 each) (BAY 1841788 Tables for Risk Management Plan, Table 1/3 dated 05 SEP 2022). Similarly, no difference was observed between the treatment arms when excluding the superficial skin cancers (Table SVII.5).

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Table SVII.4: Incidence of all Second Primary Malignancies during treatment and in follow-up period in the ARAMIS Study- Primary completion database (Safety set)

Adverse Event Grouping Second primary malignancies'		**Darolutamide- #double-blind period (N=954) N (Rate in %) Crude Incidence Rate**	**Placebo- #double-blind period (N=554) N (Rate in %) Crude Incidence Rate**
Adverse events	All 95% CI for rate (%)	27 (2.8) (1.87, 4.09)	16 (2.9) (1.66, 4.65)
	Grade 1	2 (0.2)	4 (0.7)
	Grade 2	10 (1.0)	3 (0.5)
	Grade 3	12 (1.3)	9 (1.6)
	Grade 4	2 (0.2)	0
	Grade 5	1 (0.1)	0
	Risk ratio 95% CI for risk ratio	0.98 (0.53, 1.80)	
	EAIR (per 100 patient years) (95 % CI for EAIR)	2.0 (1.33, 2.94)	2.8 (1.61, 4.58)
Adverse event recovered/resolved	All	9 (0.9)	8 (1.4)
Adverse event leading to hospitalisation	All	14 (1.5)	5 (0.9)
Adverse event with fatal outcome	All	1 (0.1)	0
SAEs	All 95% CI for rate (%)	20 (2.1) (1.29, 3.22)	8 (1.4) (0.63, 2.83)
	EAIR (per 100 patient years) (95 % CI for EAIR)	1.5 (0.91, 2.31)	1.4 (0.61, 2.78)
AE leading to darolutamide/placebo dose reduction	All	0	0
AE leading to permanent darolutamide/placebo discontinuation	All	10 (1.0)	6 (1.1)

Abbreviations: AE = Adverse event; CI = Confidence Interval, EAIR = exposure-adjusted incidence rate, N = Number; SAE = Serious adverse events

Source: Module 5.3.5.3 Tables for Risk Management Plan, Table 1/1

Note: Secondary primary malignancies are defined by SMQ Malignant tumours excluding PTs starting with 'Prostate cancer', PTs in HLGT Metastases, PT Cancer in remission and LLT Progression of pre-existing cancer.

Note: A patient is counted as 'recovered/resolved' if for this patient all adverse events (preferred terms) belongi ng to the event of interest are resolved.

Note: MedDRA Version 25.0, CTCAE Version 4.03

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Table SVII.5: Incidence of Second Primary Malignancies excluding superficial skin cancers during treatment and in follow-up period in the ARAMIS Study (Safety set)

Adverse Event Grouping Second primary malignancies excluding superficial skin cancers		Darolutamide- #double-blind period (N=954) N (Rate in %) Crude Incidence Rate	Placebo- #double-blind period (N=554) N (Rate in %) Crude Incidence Rate
Any event	Any MedDRA PT term	20 (2.1%)	13 (2.3%)
	EAIR (per 100 patient years)	1.5	2.3
	Risk ratio 95% CI for risk ratio	0.89 (0.45, 1.78)	
	Risk difference 95% CI for risk difference	0.003 (-0.013, 0.018)	
	Incidence Risk ratio for EAIR	0.65	

Abbreviations: CI = confidence interval, EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; PT = Preferred Term.

Source: BAY 1841788 Tables for Risk Management Plan, Table 1/3 dated 15 SEP 2022

Exposure-adjusted incidence rate (EAIR) of TEAEs, defined as the number of patients with a given TEAE divided by the total darolutamide/placebo treatment duration of all patients in years. The rate is expressed in 100 patient years.
Treatment duration (years) = treatment duration (weeks)*7 divided by 365.25.
Note: This table contains counts of patients. If a patient experienced more than one episode of an adverse event, the patient is counted only once within a preferred term. Patients may have more than one entry.
Note: Secondary primary malignancies include one event starting 33 days after last dose (placebo).
MedDRA version 25.0
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Phase 3 Study 17777 (ARASENS):

A summary of the incidence of SPM AEs during the treatment and in follow-up period is presented in Table SVII.6 below.

The incidence of SPM AEs was 3.8% in the darolutamide + docetaxel arm and 2.5% in the placebo + docetaxel arm. Out of the 25 patients with SPM AEs in the darolutamide + docetaxel arm, the most frequently reported PTs (≥2) included basal cell carcinoma (n=3), squamous cell carcinoma of the skin, pancreatic carcinoma, squamous cell carcinoma (all n=2 each) (BAY 1841788 Tables for Risk Management Plan, Table 1/7 dated 05 SEP 2022).

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Table SVII.6: Incidence of all Second Primary Malignancies during treatment and in follow-up period in the ARASENS Study- Primary completion database (Safety set)

Adverse Event Grouping Second primary malignancies		**Darolutamide- #double-blind period (N=652) N (Rate in %) Crude Incidence Rate**	**Placebo- #double-blind period (N=650) N (Rate in %) Crude Incidence Rate**
Adverse events	All 95% CI for rate (%)	25 (3.8) (2.50, 5.61)	16 (2.5) (1.41, 3.97)
	Grade 1	2 (0.3)	2 (0.3)
	Grade 2	7 (1.1)	7 (1.1)
	Grade 3	9 (1.4)	6 (0.9)
	Grade 4	3 (0.5)	0
	Grade 5	4 (0.6)	1 (0.2)
	Risk ratio 95% CI for risk ratio	1.56 (0.84, 2.89)	
	EAIR (per 100 patient years) (95 % CI for EAIR)	1.4 (0.93, 2.13)	1.3 (0.76, 2.16)
Adverse event recovered/resolved	All	10 (1.5)	8 (1.2)
Adverse event leading to hospitalisation	All	6 (0.9)	5 (0.8)
Adverse event with fatal outcome	All	4 (0.6)	1 (0.2)
SAEs	All 95% CI for rate (%)	15 (2.3) (1.29, 3.77)	11 (1.7) (0.85, 3.01)
	EAIR (per 100 patient years) (95 % CI for EAIR)	0.9 (0.49, 1.43)	0.9 (0.46, 1.64)
AE leading to darolutamide/placebo dose reduction	All	0	0
AE leading to permanent darolutamide/placebo discontinuation	All	9 (1.4)	4 (0.6)

Abbreviations: AE = Adverse event; CI = Confidence Interval, EAIR = exposure-adjusted incidence rate; N = Number; SAE = Serious adverse events

Source: Module 5.3.5.3 Tables for Risk Management Plan, Table 1/6

Note: Secondary primary malignancies are defined by SMQ Malignant tumours excluding PTs starting with 'Prostate cancer', PTs in HLGT Metastases, PT Cancer in remission and LLT Progression of pre-existing cancer.

Note: A patient is counted as 'recovered/resolved' if for this patient all adverse events (preferred terms) belongin g to the event of interest are resolved.

Note: MedDRA Version 25.0, CTCAE Version 4.03

Global Integrated Analysis: /var/swan/root/bhc/1841788/ia/stat/query05/prod/pgms/t_ema_adae_eoi_arasens.sa s 05SEP2022 18:26

Table SVII.7: Incidence of Second Primary Malignancies excluding superficial skin cancers during treatment and in follow-up period in the ARASENS Study (Safety set)

Adverse Event Grouping Second primary malignancies excluding superficial skin cancers		Darolutamide-#double-blind period (N=652) N (Rate in %) Crude Incidence Rate	Placebo-#double-blind period (N=650) N (Rate in %) Crude Incidence Rate
Any event	Any MedDRA PT term	19 (2.9%)	13 (2.0%)
	EAIR (per 100 patient years)	1.1	1.1
	Risk ratio 95% CI for risk ratio	1.46 (0.73, 2.93)	
	Risk difference 95% CI for risk difference	-0.009 (-0.026, 0.008)	
	Incidence Risk ratio for EAIR	1.01	

Abbreviations: CI = confidence interval, EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; PT = Preferred Term.

Source: Source: BAY 1841788 Tables for Risk Management Plan, Table 1/8 dated 05 SEP 2022

Note: Secondary primary malignancies are defined by SMQ Malignant tumours excluding PTs starting with 'Prostate cancer', PTs in HLGT Metastases, PT Cancer in remission and LLT Progression of pre-existing cancer.
Exposure-adjusted incidence rate (EAIR) of TEAEs, defined as the number of patients with a given TEAE divided by the total darolutamide/placebo treatment duration of all patients in years. The rate is expressed in 100 patient years.
Treatment duration (years) = treatment duration (weeks)*7 divided by 365.25.
Note: This table contains counts of patients. If a patient experienced more than one episode of an adverse event, the patient is counted only once within a preferred term. Patients may have more than one entry.
Global Integrated Analysis: /var/swan/root/bhc/1841788/ia/stat/query05/prod/pgms/t_ema_14_3_1_adae_s3_11_expadj_special_nonstrat_upd.sas 16SEP2022 15:09

Phase 3 Study 21140 (ARANOTE):

SPMs were reported up to 30 days after the last dose of the study drug, after which only additional primary tumours regarded as related to the study drug were reported.

SPMs during the treatment period were reported with a comparable incidence between the darolutamide and placebo arms (2.7% and 0.9%, respectively). After adjusting by study drug treatment exposure, the EAIR was 1.5 vs. 0.6 (Table SVII.8).

SPMs reported in ≥2 patients the darolutamide arm are summarised below.

- Bladder cancer: 2 participants (0.4%) vs. 1 participant (0.5%)
- Squamous cell carcinoma of skin: 2 participants (0.4%) vs. 0 participants

It is important to note that the case reporting Bowen’s disease with darolutamide described a non-malignant condition.

The most common TEAEs of SPMs were reported with a worst CTCAE grade of Grade 2 or 3.

Table SVII.8: Treatment-emergent additional primary malignancies (SAF)

MedDRA PT	Darolutamide N=445		Placebo N=221	
	Total n (%)	EAIR per 100 PY[a]	Total n (%)	EAIR per 100 PY[a]
Any	12 (2.7)	1.5	2 (0.9)	0.6
Bladder cancer	2 (0.4)	0.2	1 (0.5)	0.3
Squamous cell carcinoma of skin	2 (0.4)	0.2	0	0
Adenocarcinoma of colon	1 (0.2)	0.1	0	0
Basal cell carcinoma	1 (0.2)	0.1	0	0
Bowen's disease	1 (0.2)	0.1	0	0
Diffuse large B-cell lymphoma	1 (0.2)	0.1	0	0
Malignant melanoma	1 (0.2)	0.1	0	0
Rectal cancer	1 (0.2)	0.1	0	0
Renal cell carcinoma	1 (0.2)	0.1	0	0
Squamous cell carcinoma of lung	1 (0.2)	0.1	0	0
Bladder cancer recurrent	0	0	1 (0.5)	0.3
Lung carcinoma cell type unspecified stage IV	0	0	1 (0.5)	0.3

Abbreviations: EAIR = Exposure-adjusted incidence rate; EOT = End of treatment; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of participants (100%); n = Number of participants with event; PT = Preferred term; PY=Participant year; SAF = Safety analysis set

[a]: EAIR was defined as the number of participants with the event divided by the sum of the exposure times, where the exposure time was the time to the first occurrence if an event occurred; otherwise it was the treatment duration and time at risk after treatment end, where time at risk after treatment end = time after the EOT up to minimum of death date, data cut-off,withdrawal from study, EOT-emergent window, or lost to follow-up.

Note: A participant may have >1 entry.

MedDRA v. 27.0

Source: Table 8.3.2/12

In the ARANOTE + ARAMIS pool, both the crude incidences (2.8% vs. 2.2%) as well as the EAIRs (1.8 vs. 1.8 per 100 PY) were similar in both treatment arms.

No particular neoplasm or cluster of neoplasms was identified in either ARANOTE or the pool, as having an increased incidence in the darolutamide arm compared to the placebo arm. In conclusion, there was insufficient evidence to support a causal relationship between the occurrence of SPMSs and the administration of darolutamide.

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Post-marketing data excluding pivotal trials (ARAMIS, ARASENS and ARANOTE)*:*

Retrieval criteria

A search was performed in the Bayer Global Safety Database for the events coded to MedDRA SMQ Malignant tumours, excluding PTs Hormone-refractory prostate cancer, Hormone-dependent prostate cancer, Neoplasm prostate, Prostate cancer, Prostate cancer metastatic, Prostate cancer recurrent, Prostate cancer stage 0, Prostate cancer stage I, Prostate cancer stage II, Prostate cancer stage III, Prostate cancer stage IV, Cancer in remission, Neoplasm malignant, Recurrent cancer, Metastatic neoplasm, Malignant neoplasm progression, Progression of pre-existing cancer, and all PTs from HLGT Metastases.

Case presentation:

The search yielded 102 cases received *cumulatively* from all post-marketing sources since market launch (30 JUL 2019) up to 30 JAN 2024. Twelve cases (12, 11.8%) were received from spontaneous reports, 27 cases (26.5%) were received from interventional studies, and 63 cases (61.8%) were received from observational studies.

All reports originated from the following countries: US (52 reports), Japan (20 reports), France (8 reports), Canada (5 reports), Australia and Spain (4 reports each), Colombia and South Korea (3 reports each), Brazil, Germany, and Switzerland (1 report each). Fifty-one (51) cases (50.0%) were medically confirmed, and 51 cases (50.0%) were non-medically confirmed. Ninety-five (95) cases were serious and 7 cases were non-serious.

The 102 reported cases included 112 events of SPMs. Table SVII.9 depicts the list of PTs of second primary malignancy. The most commonly reported (≥3) PTs were Bone cancer (13), Lung neoplasm malignant (6), Malignant melanoma (6), and Pancreatic carcinoma (6).

Table SVII.9: Tabulation by Preferred Term for all relevant carcinogenicity potential events that met retrieval criteria reported cumulatively from all post-marketing sources since 30 JUL 2019 up to 30 JAN 2024

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
All AEs	**7**	**105**	**112**
Bone cancer	0	13	13
Lung neoplasm malignant	3	3	6
Malignant melanoma	0	6	6
Pancreatic carcinoma	0	6	6
Bladder cancer	0	4	4
Skin cancer	0	4	4
Adenocarcinoma of the colon	0	3	3
Colon cancer	0	3	3
Gastric cancer	0	3	3
Hepatic cancer	0	3	3
Lymphoma	0	3	3
Squamous cell carcinoma	1	2	3

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Table SVII.9: Tabulation by Preferred Term for all relevant carcinogenicity potential events that met retrieval criteria reported cumulatively from all post-marketing sources since 30 JUL 2019 up to 30 JAN 2024

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
Transitional cell carcinoma	0	3	3
Basal cell carcinoma	0	2	2
Bile duct cancer	0	2	2
Colorectal adenocarcinoma	0	2	2
Hepatocellular carcinoma	1	1	2
Liposarcoma	2	0	2
Rectal cancer	0	2	2
Renal cancer	0	2	2
Salivary gland cancer	0	2	2
Small cell lung cancer	0	2	2
Thyroid cancer	0	2	2
Acute myeloid leukaemia	0	1	1
Adenocarcinoma gastric	0	1	1
Bladder cancer recurrent	0	1	1
Bladder transitional cell carcinoma	0	1	1
Breast cancer metastatic	0	1	1
Cancer with a high tumour mutational burden	0	1	1
Chronic lymphocytic leukaemia	0	1	1
Clear cell renal cell carcinoma	0	1	1
Colorectal cancer	0	1	1
Epithelioid mesothelioma	0	1	1
Gastric cancer recurrent	0	1	1
Gastric neuroendocrine carcinoma	0	1	1
Gastrointestinal neuroendocrine carcinoma	0	1	1
Glioblastoma	0	1	1
Head and neck cancer	0	1	1
Hepatic neuroendocrine tumour	0	1	1
Hodgkin's disease	0	1	1
Lung adenocarcinoma	0	1	1
Lymphocytic leukaemia	0	1	1
Malignant neoplasm of renal pelvis	0	1	1
Malignant pleural effusion	0	1	1
Non-small cell lung cancer	0	1	1
Pancreatic carcinoma metastatic	0	1	1
Plasma cell myeloma	0	1	1

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Table SVII.9: Tabulation by Preferred Term for all relevant carcinogenicity potential events that met retrieval criteria reported cumulatively from all post-marketing sources since 30 JUL 2019 up to 30 JAN 2024

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
Small cell carcinoma	0	1	1
Soft tissue sarcoma	0	1	1
Throat cancer	0	1	1

Abbreviations: AE =Adverse event.

The review of the data shows that the reported SPM events originated from broad post-marketing sources and countries. Twelve (12) events in total reported a fatal outcome (Breast cancer metastatic, Pancreatic carcinoma, Small cell lung cancer, Malignant pleural effusion, Adenocarcinoma gastric, Gastric neuroendocrine carcinoma, Hepatic neuroendocrine tumour, Glioblastoma, Epithelioid mesothelioma, Bladder cancer, Bone cancer, and Hepatic cancer).

Overall, the review of the reported carcinogenicity events did not identify a specific pattern of malignancy, as these were mostly single events, or potentially related to prostate cancer (bone cancer).

Risk factors and risk groups:

As described in literature, risk factors include radiation, tobacco use, alcohol use, high-body-mass index, and high fasting plasma glucose (74, 75).

Preventability:

No known preventive measures.

Impact on the risk-benefit balance of the product:

Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact:

At present public health impact is limited.

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SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing information: Use in patients with severe renal impairment

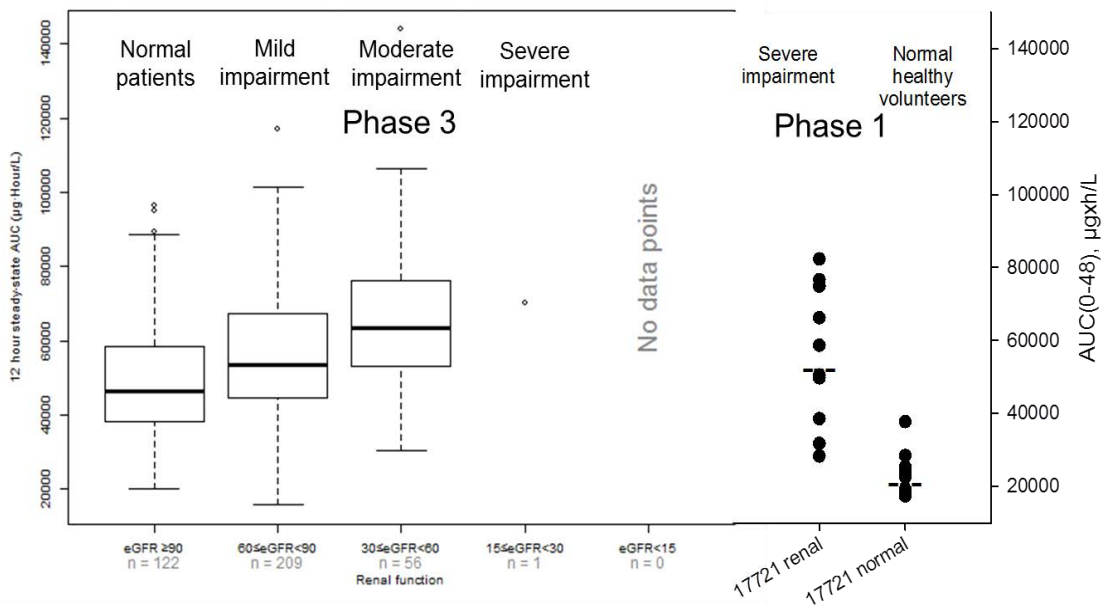
Evidence source:

As patients with SCR ≥2.0 x ULN at screening visit were not eligible for inclusion in the pivotal Phase 3 Study 17712 (ARAMIS), only one patient with severe renal impairment whose renal function deteriorated during the treatment period was included in nmCRPC pool.

Based on the single dose data in non-cancer subjects a 2.5-fold increase of darolutamide exposure $AUC_{(0-48)}$ was observed in subjects with severe renal impairment compared to healthy, age- and body weight-matched male subjects (Study 17721).

The population PK analysis of the data from the Phase 3 Study 17712 suggests a 1.1-fold increase in darolutamide exposure for nmCRPC patients with mild renal impairment and in 1.3-fold increase in darolutamide exposure for patients with moderate renal impairment (see Figure SVII.2).

Figure SVII.2: Comparison of steady-state AUC(0-12)ss in nmCRPC patients stratified by renal function according to NCI criteria from Phase 3 Study 17712 and single dose AUC(0-48) in male volunteers stratified by renal function from Study 17721



Abbreviations: AUC(0-48) = area under the plasma concentration time curve from 0 to 48 hours post dose; AUC(0-12)ss = area under the plasma concentration-time curve from 0 to 12 hours after nominal BID dosing to steady state; BID = *bis in die*; IQR = inter quartile range; NCI = National Cancer Institute; nmCRPC = non-metastatic castration-resistant prostate cancer.

Each box covers the IQR, with the median as the vertical black line inside the box, and with the whiskers extending to the last data point within the 1.5 times the IQR.

Analysis of safety data from the Study 17712 revealed that the incidence of grade 5 events and SAEs in each renal function subgroup was similar between the arms.

The analysis of the relationship between the exposure [$AUC_{(0\ 12)ss}$] of darolutamide (based on PK subgroup of 388 patients of Study 17712 and population PK model) and the incidence rate of ADRs (grouped term 'fatigue/asthenic conditions'; grouped term 'rash' and PT pain in extremity) did not reveal correlation between the incidence of ADRs and the exposure [$AUC_{(0\ 12)ss}$] of darolutamide. The overall incidence of TEAEs considered as ADRs for darolutamide was similar among the different exposure quartiles – 12.1%, 15.5%, 17.2% and 13.4% for exposure quartiles 1, 2, 3 and 4, respectively. The incidence of ADRs by worst grade was also similar between the different exposure quartile subgroups.

Additionally, no relationship was found between darolutamide exposure and increase of serum bilirubin in patients participating in the Study 17712.

In the ARASENS (Study 17777), one patient (<0.1%) in the darolutamide + docetaxel arm had severe renal impairment at baseline based on eGFR but was eligible based on a SCR level below ≤2.0 x ULN.

A 1.27-fold (90% CI: [1.14; 1.41]) higher geometric mean AUC(0–12)ss in mHSPC patients with moderate renal impairment and 1.11-fold (90% CI: [1.06; 1.17]) higher geometric mean AUC(0–12)ss in patients with mild renal impairment were identified compared with patients with normal renal function. The AUC(0–12)ss of the single mHSPC patient with severe renal impairment was approximately 2.6-fold higher compared with mHSPC patients with normal renal function, which is numerically higher compared with the 1.5-fold higher exposure in the single nmCRPC patient with severe renal impairment in Study 17712. While data from one patient with severe renal impairment only is not sufficient for robust assessment, the 2.6-fold difference in this mHSPC patient was consistent with the 2.5-fold higher exposure reported in non-cancer subjects with severe renal impairment than in subjects with a normal renal function.

Overall, the identified higher exposures in both nmCRPC (Study 17712) and mHSPC (Study 17777) patients with mild or moderate renal impairment is not considered clinically relevant. In addition, there was very limited information from Phase 3 studies regarding the impact of severe renal impairment (1.5 and 2.6-fold higher exposure in the single nmCRPC patient from Study 17712 and the single mHSPC patient from Study 17777, respectively).

In a separate Phase 1 study in non-cancer subjects (Study 17721), a 2.5-fold higher exposure was reported in subjects with severe renal impairment (n=10) than in subjects with normal renal function.

In conclusion, the current results regarding the impact of renal impairment in Study 17777 are generally consistent with those previously reported. No darolutamide dose adjustment is needed for mHSPC patients with mild or moderate renal impairment.

In addition, there were no clinically meaningful differences in the incidence of TEAEs between the renal function groups or between the treatment arms (darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT), suggesting that there

is no increased risk for renal function-related undesirable effects of treatment with darolutamide in combination with docetaxel and ADT.

Phase 3 Study 21140 (ARANOTE):

There were no participants enrolled in the study with severely impaired renal function at baseline.

There were no clinically meaningful differences in the incidence of TEAEs between the renal function groups or between the treatment arms (darolutamide + ADT versus placebo + ADT), suggesting that there is no increased risk for renal function-related undesirable effects of treatment with darolutamide in combination with ADT.

Anticipated risk/consequence of the missing information:

1.5 and 2.6-fold higher exposure of darolutamide may be expected in nmCRPC and mHSPC patients with severe renal impairment. It is uncertain whether cancer patients with severe renal impairment may be at higher risk for ADRs when exposed to darolutamide in comparison to the general target population.

Based on the limited patient data and the evaluation in non-cancer subjects (Study 17721), a starting dose of 300 mg darolutamide BID is recommended for patients with severe renal impairment.

Post-marketing data excluding pivotal trials (ARAMIS, ARASENS and ARANOTE)*:*

Retrieval criteria:

Reports of patients with a medical history of severe renal failure coded to Standardised MedDRA Query (SMQ) Acute renal failure and SMQ Chronic kidney disease.

The search strategy yielded 237 cases received *cumulatively* from post-marketing sources since market launch (30 JUL 2019) up to 30 JAN 2024 that met the above search criteria. Of these 237 cases, 127 cases (53.6%) were serious and 110 cases (46.4%) were non-serious. One hundred thirty-four (134) cases (56.5%) were medically confirmed and 103 cases (43.5%) were non-medically confirmed. Of these 237 cases, 31 cases (13.1%) were derived from spontaneous reports, 33 cases (13.9%) were from interventional studies and 173 cases (73.0%) from observational studies (includes patient support and market research programs).

Most patients were ≥65 years old (207, 87.3%), 21 (8.9%) were adults (≥18 years and <65 years), and for 9 patients (3.8%) the age group was unknown.

Analysis of the PTs of medical history of potentially severe renal impairment revealed that almost half of the patients (n=124, 41.8%) had Chronic kidney disease, with Acute kidney injury being the second most reported PT (n=39, 13.1%). Further medical history PTs were reported in <10% of patients.

Cumulatively, among 237 cases identified with a history of potentially severe renal failure, 620 AEs were reported (Table SVII.10). The most commonly reported AEs were Fatigue (n=44), Off-label use (n=28), Asthenia (n=19), Product dose omission issue, Prostatic specific antigen increased, Hot flush (n=13 each), and Decreased appetite (n=10). All other PTs were

reported at a frequency of <10 events. Overall, the most commonly reported AEs are known to occur after the administration of darolutamide or they are related to the concurrent administration of ADT, or they are related to the underlying prostate malignancy. This is similar to the AEs reported in the general patient population.

Table SVII.10: Events reported at a frequency of ≥4 in patients with a history of renal impairment, by Preferred Term

Preferred Term	Non-serious AEs[1]	Serious AEs[1]	Total AEs[1]
All AEs	**406[1]**	**214[1]**	**620[1]**
Fatigue	43	1	44
Off label use	28	0	28
Asthenia	16	3	19
Product dose omission issue	13	0	13
Prostatic specific antigen increased	10	3	13
Hot flush	13	0	13
Decreased appetite	7	3	10
Diarrhoea	8	1	9
Dizziness	6	3	9
Pain in extremity	8	0	8
Nausea	8	0	8
Arthralgia	8	0	8
Renal impairment	0	8	8
Rash	6	1	7
Acute kidney injury	0	7	7
Anaemia	4	3	7
Pain	6	0	6
Constipation	5	1	6
Blood creatinine increased	5	1	6
Death	0	6	6
Renal failure	0	5	5
Dehydration	1	4	5
Muscular weakness	5	0	5
Urinary tract infection	0	5	5
Sepsis	0	5	5
Headache	4	1	5
Vomiting	3	2	5
Malaise	4	0	4
Drug ineffective	4	0	4
Somnolence	4	0	4

Table SVII.10: Events reported at a frequency of ≥4 in patients with a history of renal impairment, by Preferred Term

Preferred Term	Non-serious AEs[1]	Serious AEs[1]	Total AEs[1]
Abdominal pain	4	0	4
Illness	4	0	4
Bone pain	3	1	4
Dyspnoea	3	1	4
Weight increased	4	0	4
Fall	1	3	4
Pruritus	4	0	4
Hormone-refractory prostate cancer	0	4	4
Hypertension	3	1	4

[1]Note that the numbers of events for the individual PTs do not add up to the overall number of "all AEs", as not all events are shown. Only those PTs that were reported with a frequency of ≥3 events are shown.
Abbreviations: AE = Adverse event.

Conclusion

Based on the review of the reports, the analysis does not reveal that the safety profile of darolutamide in patients with potentially severe renal impairment is different from that in the general target population.

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Part II: Module SVIII - Summary of the safety concerns

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	ADRs resulting from increased exposure in patients with severe hepatic impairment Cardiovascular events in patients with significant CV history Carcinogenicity potential
Missing information	Use in patients with severe renal impairment

Abbreviations: ADR = Adverse drug reaction; CV = Cardiovascular.

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No important identified risks have been associated with Nubeqa. Routine pharmacovigilance activities are in place for the important potential risks and missing information of Nubeqa and will be conducted as detailed in corresponding pharmacovigilance procedures that are in place at Bayer. These routine activities include the collection, follow--up, evaluation, and expedited reporting of individual case reports, ongoing monitoring and signal investigation, as well as preparation of Periodic Benefit-Risk Evaluation Reports/Periodic Safety Update Reports.

III.1.1 Specific adverse reaction follow-up questionnaires for safety concerns

Targeted follow-up questionnaires are in place for Nubeqa:

- Questionnaire for use in patients with history of hepatic impairment
- Questionnaire for use in patients with history of renal impairment
- Questionnaire for cardiac disorders
- Questionnaire for carcinogenicity potential

The forms are provided in Annex 4 of this RMP.

III.1.2 Other forms of routine pharmacovigilance activities for safety concerns

Updates on important potential risks and missing information will be provided in each Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report, if new safety relevant information is received during the period of the report.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities currently in place for Nubeqa.

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Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.3 Summary table of additional pharmacovigilance activities

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

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Status				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies with darolutamide are currently ongoing or planned.

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

No important identified risks have been associated with Nubeqa.

The risk minimisation measures for the safety concerns associated with Nubeqa comprise the following routine risk minimisation measures:

- Routine risk communication messages to communicate the risks to healthcare professionals and patients, so that an informed decision can be made.
- Routine risk communication messages recommending specific clinical measures to address the safety concerns.
- Other routine measures beyond the product information, *i.e.*, Nubeqa is a prescription-only medicine.

By these measures, the safety concerns associated with Nubeqa are appropriately managed to be acceptable for a positive benefit-risk balance. No risk minimisation measures beyond routine are deemed necessary.

V.1 Routine risk minimisation measures

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

Safety concern	Routine risk minimisation measures
Important potential risks	
ADRs resulting from increased exposure in patients with severe hepatic impairment	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.8 Undesirable effects SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warnings and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

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

Safety concern	Routine risk minimisation measures
Cardiovascular events in patients with significant CV history	**Routine risk communication** SmPC section 5.1 Pharmacodynamic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine
Carcinogenicity potential	**Routine risk communication** SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk** None proposed **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine
Missing information	
Use in patients with severe renal impairment	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warnings and precautions for use SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine

Abbreviations: ADRs= Adverse Drug Reactions; CV = Cardiovascular; SmPC = Summary of Product Characteristics.

V.2 Additional risk minimisation measures

The safety concerns associated with Nubeqa are appropriately managed by routine risk minimisation measures to be acceptable for a positive benefit-risk balance. Thus, no additional risk minimisation measures are deemed necessary.

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EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.3 Summary of risk minimisation measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
ADRs resulting from increased exposure in patients with severe hepatic impairment	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.8 Undesirable effects SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Updates on important potential risks will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Follow-up questionnaire in patients with history of hepatic impairment.
Cardiovascular events in patients with significant CV history	**Routine risk communication** SmPC section 5.1 Pharmacodynamic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Updates on important potential risks will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Follow-up questionnaire on cardiac disorders.

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EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Carcinogenicity potential	**Routine risk communication** SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk** None proposed **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Updates will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Follow-up questionnaire on second primary malignancies
Missing information		
Use in patients with severe renal impairment	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.4: Special warnings and precautions for use SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Updates on missing information will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Follow-up questionnaire in patients with history of renal impairment.

Abbreviations: ADRs = Adverse Drug Reactions; CV = Cardiovascular; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for Nubeqa (Darolutamide)

This is a summary of the RMP for Nubeqa. A Risk Management Plan (RMP) details important risks, how these risks can be minimised, and how more information will be obtained about these risks and uncertainties (missing information).

Nubeqa's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nubeqa should be used.

This summary of the RMP for Nubeqa 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 Nubeqa's RMP.

I. The medicine and what it is used for

Nubeqa is authorised for the treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see SmPC for the full indication) and for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy. It contains darolutamide as the active substance and it is administered orally.

Further information about the evaluation of Nubeqa's benefits can be found in Nubeqa's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/nubeqa.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

No important identified risks are known for Nubeqa at this point in time. All identified risks are classified as non-important and are managed by the following *routine risk minimisation measures*:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- The medicine's legal status — the way a medicine is supplied to the patient (*e.g.*, with or without prescription) can help to minimise its risks.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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Part VI: Summary of the risk management plan

If important information that may affect the safe use of Nubeqa is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nubeqa are risks that need special risk management activities to further investigate or minimise 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 Nubeqa. 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).

Table Part VI.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	Adverse drug reactions resulting from increased exposure in patients with severe hepatic impairment Cardiovascular events in patients with significant cardiovascular history Carcinogenicity potential
Missing information	Use in patients with severe renal impairment

II.B Summary of important risks

Important potential risk: ADRs resulting from increased exposure in patients with severe hepatic impairment	
Evidence for linking the risk to the medicine	It is uncertain whether patients with moderate to severe hepatic impairment may be at higher risk of adverse drug reactions (ADRs) when exposed to darolutamide in comparison to general target population. Patients with active viral hepatitis, active human immunodeficiency virus (HIV), chronic liver disease or with screening values of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥2.5 x ULN, total bilirubin ≥1.5 x ULN (except patients with a diagnosis of Gilbert's disease) were not eligible for inclusion in the pivotal Phase 3 Studies 17712 (ARAMIS) and 17777 (ARASENS). Based on the single dose data in non-cancer patients a 1.9-fold increase in darolutamide exposure area under the curve ($AUC_{(0-48)}$) was observed in 9 subjects with moderate hepatic impairment compared to 10 healthy, age- and body weight-matched subjects (Study 17721, using Child-Pugh categorisation system for hepatic impairment).

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Important potential risk: ADRs resulting from increased exposure in patients with severe hepatic impairment	
Risk factors and risk groups	Patients with impaired hepatic function.
Risk minimisation measures	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.8 Undesirable effects SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

Important potential risk: Cardiovascular events in patients with significant CV history	
Evidence for linking the risk to the medicine	The androgen deprivation therapy (ADT) associated changes in body composition, lipids, and insulin sensitivity are suspected to increase the risk for diabetes and cardiovascular disorders in prostate cancer patients. The overall evidence is, however, conflicting and the relationship between ADT and cardiovascular disorders remains unclear. Patients with recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV were excluded from the pivotal clinical Studies 17712 (ARAMIS) and 17777 (ARASENS). It is uncertain whether patients with the medical history of recent significant cardiovascular events may be at higher risk for cardiovascular disorders (progression) in association with darolutamide exposure.
Risk factors and risk groups	Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and congestive heart failure NYHA Class III or IV.

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Important potential risk: Cardiovascular events in patients with significant CV history	
Risk minimisation measures	**Routine risk communication** SmPC section 5.1 Pharmacodynamic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

Important potential risk: Carcinogenicity potential	
Evidence for linking the risk to the medicine	In the pivotal Phase 3 clinical trials ARAMIS (Study 17712) and ARASENS (Study 17777), a slight numerical imbalance was only observed in the incidence of all second primary malignancies in the darolutamide + docetaxel arm compared to the placebo + docetaxel arm in Study 17777. However, after adjusting for study treatment duration, the exposure-adjusted incidence rate (EAIR) per 100 patient years was similar between treatment arms (1.4 and 1.3) in the darolutamide + docetaxel arm and placebo + docetaxel arm, respectively). Nonclinical safety data of darolutamide do not indicate a carcinogenic potential. The results of chronic toxicity studies in rats and dogs at multiples up to 4 to 5-fold the therapeutic exposure did not show signs of off target toxicity or proliferative tissue lesions indicative of a risk of secondary neoplasia following prolonged treatment with darolutamide. Also, darolutamide did not show genotoxicity *in vitro* and *in vivo.* In the pivotal 26-week carcinogenicity study with orally administered darolutamide in 001178-T (hemizygous) RasH2 mice, no darolutamide-related effects were noted on the incidence or type of neoplasms. At the maximum feasible dose of 1,000 mg/kg/day, exposure was 0.9 - 1.3 times the clinical exposure in humans at the therapeutic dose of 600 mg BID. In conclusion, no carcinogenic potential was observed up to the highest darolutamide dose administered in the carcinogenicity study. Taking into account the darolutamide exposure in this study within the range of clinical exposure, this study may not fully exclude the potential risk of carcinogenicity. In 2-year carcinogenicity studies in rats with other second-generation androgen receptor inhibitor drugs in the same pharmacological class as darolutamide, neoplastic findings of unknown relevance to humans were observed.

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Important potential risk: Carcinogenicity potential	
Risk factors and risk groups	As described in literature, risk factors include radiation, tobacco use, alcohol use, high body mass index, and high fasting plasma glucose.
Risk minimisation measures	**Routine risk communication** SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk** None proposed **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warnings and precautions for use SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Nubeqa.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Nubeqa.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Targeted follow-up questionnaires for spontaneous case reports are in place for the following safety concerns:

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

Not applicable.

QUESTIONNAIRE FOR USE IN PATIENTS WITH HISTORY OF HEPATIC IMPAIRMENT

Dear Doctor,

Pharmacovigilance activities are a standard requirement in drug development and post-marketing surveillance. The main purpose is to monitor and manage safety risks and to provide appropriate safety information to the patients, the prescribers/physicians and the regulatory agencies. The purpose of this questionnaire is to collect complementary pertinent information about the event you reported in a patient with history of hepatic impairment. Your contribution will help improve the knowledge on the safety profile of darolutamide Thank you very much for your cooperation.

→ **Please fill in the open fields only (those that are not struck out), and answer all the 'Yes/No' questions. The purpose is to collect data that were not available at the time of the first report.**

→ **Please note: For clinical studies, this questionnaire does not replace the CRF. Data reported in this questionnaire must be noted as appropriate in the CRF of the study.**

→ **We kindly ask you to return the completed form to the Bayer local Pharmacovigilance Office as soon as the event has improved / resolved (e.g. once the patient is discharged from hospital); or within 4 weeks if the event is ongoing.**

Patient Demographic Information (to be filled in by PV case processing)

Gender: Male [ ] Female [ ]

Ethnicity: Asian [ ] Caucasian [ ] Black [ ] Hispanic [ ] Unknown [ ] Other [

Age (years): _____

Weight (kg): _____

Height (m): _____

Study Information

Global Case ID;

Study ID: Study Center Patient ID:

Underlying disease (study indication)

Details of Adverse Drug Reaction

Event (verbatim)	Start date (dd/MMM/yy)	Stop date (dd/MMM/yy

1. Confirm timing of Adverse Drug Reaction

	Day	Month	Year
Date of first dose of darolutamide			
Date of last dose of darolutamide			
Onset date of liver dysfunction event			

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2. Concomitant medications

Did the patient receive any other drugs *within 1 month* prior to onset of the Adverse Drug Reaction? Yes □ / No □

If any other drugs were taken within 1 month of the onset, please provide a full list of these drugs, including any analgesics, general anaesthetic agents, herbal medicines and non-prescription medications.

If a printed record is available, you may provide it with this report. (If the space below is not sufficient, please continue in the space provided at the end of the report)

Drug name / Trade name	Total daily dose	Start date	Stop date	Indication

Do you consider any of the concomitant drugs as a possible/contributing cause for the reported Adverse Drug Reaction?

Yes □ / No □

If yes, please specify which drug(s)_____

3. Medical History

Are any of the events/ conditions listed below known from the patient's past medical history? Yes ☐ / No ☐

If yes, please provide details below.

Condition / event (please tick all that apply)		Date of onset	Cured or resolved?	If cured or resolved: Stop date
Liver Metastasis	☐	_____	Yes ☐ / No ☐	_____
Liver cirrhosis / fibrosis	☐	_____	Yes ☐ / No ☐	_____
(If yes, Child-Pugh Class: ____)				
Fatty liver (hepatic steatosis)	☐	_____	Yes ☐ / No ☐	_____
Viral Hepatitis	☐	_____	Yes ☐ / No ☐	_____
Hepatic vein thrombosis	☐	_____	Yes ☐ / No ☐	_____
Alcohol misuse	☐	_____	Yes ☐ / No ☐	_____
Biliary disease (gall stones)	☐	_____	Yes ☐ / No ☐	_____
Pancreatitis	☐	_____	Yes ☐ / No ☐	_____
Autoimmune disease (specify)	☐	_____	Yes ☐ / No ☐	_____
Diabetes mellitus	☐	_____	Yes ☐ / No ☐	_____
I. v. drug abuse	☐	_____	Yes ☐ / No ☐	_____
Other (please specify):	☐	_____	Yes ☐ / No ☐	_____

Did the patient experience any of the events/ conditions listed below <u>within 1 month</u> of the onset of Adverse Drug Reaction on? Yes ☐ / No ☐

If **yes**, please provide details below.

Condition / event (please tick all that apply)		**Date of onset**	**Resolved?**	**If resolved: Stop date**
Acute cholecystitis	☐	_____	Yes ☐ / No ☐	_____
Acute *hypo*tension (If yes, specify cause: _____)	☐	_____	Yes ☐ / No ☐	_____
Acute viral infection (incl. hepatitis A,B,C, D, E, CMV, EBV, or Herpes)	☐	_____	Yes ☐ / No ☐	_____
Acute systemic infection/sepsis	☐	_____	Yes ☐ / No ☐	_____
Other (please specify):	☐	_____	Yes ☐ / No ☐	_____

4. Laboratory data: before, during and after the event

Please complete the table if the defined values are available, but had not been obtained at the time of the first SAE reporting.

		Before darolutamide **initiation**	**Last values prior to liver dysfunction**	**During the liver dysfunction event**				
Lab Test	**Units / reference range**	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__
Alk. phosphatase								
Total bilirubin								
Conjugated (direct) bilirubin								
ALT / SGPT								
AST / SGOT								
Gamma GT								
PT or INR								
LDH								
Hemoglobin								
Platelets								
WBC								
Ammonia (NH4+)								
CK								

5. Hepatitis serology

Please mark below all the hepatitis serology tests that were done and provide the results if available.

Serology test (please tick all tests that were done)		**Reference range/ units**	**Date**	**Result**
Hep. B surface Antigen	☐			
Anti-Hep. B surface Antibodies	☐			
Anti-Hep. B core Total Antibodies	☐			
Anti-Hep. B core IgM Antibodies	☐			
Anti-Hep. B core IgG Antibodies	☐			
Hepatitis B PCR (viral copies)				
Anti-Hepatitis A Virus IgM Antibodies	☐			
Anti-Hepatitis C virus Antibodies	☐			
Hepatitis C PCR (viral copies)	☐			
Anti-Cytomegalovirus (CMV) IgM Antibodies	☐			
Anti-Ebstein-Barr Virus (EBV) IgM Antibodies	☐			
Anti-nat DNA Antibodies	☐			
Anti-sm Antibodies	☐			
Anti-mitochondrial Antibodies	☐			
Other, please specify:				

6. Further information

This field provides the opportunity to provide any further information of importance in this case.

Please provide the following event details (only IF NOT PROVIDED BEFORE):

Outcome of the reported event:

Ongoing ☐ Recovered / Resolved ☐

Recovering / Resolving ☐ Not Recovered / Not Resolved ☐

Recovered with sequelae ☐ [specify: _____]

Fatal ☐ Unknown ☐

Action taken for darolutamide treatment:

Treatment discontinued permanently Yes ☐ No ☐

Treatment interrupted Yes ☐ No ☐ [If **Yes**, please provide date when treatment was restarted (if applicable): _____]

Treatment dose reduced Yes ☐ No ☐

Treatment continued without changes Yes ☐ No ☐

Causality Assessment of the event:

Related to darolutamide treatment: Yes ☐ No ☐

Please provide alternative explanation / other contributing factors: _____

Investigator's / Reporter's name..... Signature…… Date.....

QUESTIONNAIRE FOR Cardiac disorders

For use with SAE reports of Cardiac Ischemic Events

Dear Doctor,

Pharmacovigilance activities are a standard requirement in drug development and post-marketing surveillance. The main purpose is to monitor and manage safety risks and to provide appropriate safety information to the patients, the prescribers/physicians and the regulatory agencies. The purpose of this questionnaire is to collect complementary pertinent information about the case of cardiac disorders you reported. Your contribution will help improve the knowledge on the safety profile of darolutamide. Thank you very much for your cooperation.

→ **Please fill in the open fields only (those that are not struck out), and answer all the 'Yes/No' questions. The purpose is to collect data that were not available at the time of the first report.**

→ **Please note: For clinical studies, this questionnaire does not replace the CRF. Data reported in this questionnaire must be noted as appropriate in the CRF of the study.**

→ **We kindly ask you to return the completed form to the Bayer local Pharmacovigilance Office as soon as the event has improved / resolved (e.g. once the patient is discharged from hospital); or within 4 weeks if the event is ongoing.**

Patient Demographic information (to be filled in by PV case processing)

Global Case ID:

Study-ID: /centre: /patient ID:

Underlying disease (study indication):

Cardiac Ischemic Event - details

Event (verbatim)	Start date (dd/MMM/yy)	Stop date (dd/MMM/yy

Date Questionnaire issued:

Medical history

Events or diseases in the table below are known from patient's history: Yes ☐ No ☐

If **yes**, please document below.

Disease / event	Year of onset	Ongoing?	**Comment** (including ongoing treatment for disease / event)
Cardiovascular risk factors			
Hypertension		Yes ☐ / No ☐	
Hyperlipidaemia		Yes ☐ / No ☐	
Atherosclerosis		Yes ☐ / No ☐	
Diabetes mellitus		Yes ☐ / No ☐	
Smoking		Yes ☐ / No ☐	
Obesity		Yes ☐ / No ☐	
Chronic Renal Failure		Yes ☐ / No ☐	
Heart disease			
Angina pectoris		Yes ☐ / No ☐	
Myocardial infarction		Yes ☐ / No ☐	
Cardiac arrhythmia		Yes ☐ / No ☐	
Heart failure		Yes ☐ / No ☐	
Valve anomaly		Yes ☐ / No ☐	
Prosthetic valve		Yes ☐ / No ☐	
Rheumatic heart disease		Yes ☐ / No ☐	
Cerebrovascular disease			
Transient ischemic attack		Yes ☐ / No ☐	
Cerebral infarction		Yes ☐ / No ☐	
Other		Yes ☐ / No ☐	
Recent chemotherapy?		Yes ☐ / No ☐	

Is there any other relevant Medical history? Yes ☐ No ☐

If yes, please specify: _____

1. Results of other diagnostic investigations

Results of the investigations in the table below are available: Yes ☐ No ☐

If **yes**, please add results relevant to the event recorded (cardiac disorder).

Test	**Date dd/mm/yy**	**Short summary of the result** (or provide report of investigation if available)
ECG		
Cardiac Doppler sonogram		
Cardiac stress testing		
Coronary angiogram		
Other, specify		

2. Further information

This space provides the opportunity to provide any further information (including course, any alternate etiologies) of importance in this case.

3. Laboratory data: before, during and after the event

Please complete the table if the defined values are available, but had not been obtained at the time of the first SAE reporting.

		Before darolutamide initiation	Last values prior to cardiac disorder event	During the cardiac disorder event				
Lab Test	**Units / reference range**	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__	**Date** __/___/__
CK (creatinine kinase)								
CK MB								
Cardiac specific Troponin (T/ I)								
INR, or prothrombin time								
Partial thromboplastin time								
Platelets								

Please provide the following event details (only IF NOT PROVIDED BEFORE):

Outcome of the reported event:

Ongoing ☐ Recovered / Resolved ☐

Recovering / Resolving ☐ Not Recovered / Not Resolved ☐

Recovered with sequelae ☐ [specify: _____]

Fatal ☐ Unknown ☐

Action taken for darolutamide treatment:

Treatment discontinued permanently Yes ☐ No ☐

Treatment interrupted Yes ☐ No ☐ [If **Yes**, please provide date when treatment was restarted (if applicable): _____]

Treatment dose reduced Yes ☐ No ☐

Treatment continued without changes Yes ☐ No ☐

Causality Assessment of the event:

Related to darolutamide treatment: Yes ☐ No ☐

Please provide alternative explanation / other contributing factors: _____

Investigator's/ Reporter's name: _____ Signature: _____Date:

QUESTIONNAIRE FOR USE IN PATIENTS WITH HISTORY OF RENAL IMPAIRMENT

Dear Doctor,

Pharmacovigilance activities are a standard requirement in drug development and post-marketing surveillance. The main purpose is to monitor and manage safety risks and to provide appropriate safety information to the patients, the prescribers/physicians and the regulatory agencies. The purpose of this questionnaire is to collect complementary pertinent information about the case of an adverse event in a patient with **renal impairment** you reported. Your contribution will help improve the knowledge on the safety profile of darolutamide Thank you very much for your cooperation.

→ **Please fill in the open fields only (those that are not struck out), and answer all the 'Yes/No' questions. The purpose is to collect data that were not available at the time of the first report.**

→ **Please note: For clinical studies, this questionnaire does not replace the CRF. Data reported in this questionnaire must be noted as appropriate in the CRF of the study.**

→ **We kindly ask you to return the completed form to the Bayer local Pharmacovigilance Office as soon as the event has improved / resolved (e.g. once the patient is discharged from hospital); or within 4 weeks if the event is ongoing.**

Patient Demographic information (to be filled in by PV case processing)

Global Case ID:

Study-ID: /centre: /patient ID:

Ethnic origin: _____

Underlying disease (study indication):

Renal Impairment - details

Event (verbatim)	Start date (dd/MMM/yy)	Stop date (dd/MMM/yy

Date Questionnaire issued:

.

1. Confirm timing of renal impairment event

	Day	Month	Year
Date of first dose of darolutamide			
Date of last dose of darolutamide			
Onset date of renal dysfunction event			

2. Concomitant medications

Please pay special attention to any drug/substance used within the past 90 days with known side effects such as:

Name of drug	Total daily dose	Start date DD/MM/YY	Stop date DD/MM/YY	Ongoing
☐ NSAIDs				☐ Yes ☐ No ☐ Unk
☐ ACE inhibitors (please specify _____				☐ Yes ☐ No ☐ Unk
☐ Contrast agents (please specify _____				☐ Yes ☐ No ☐ Unk
☐ Antibiotics ((please specify _____				☐ Yes ☐ No ☐ Unk
☐ Cancer therapy (please specify _____				☐ Yes ☐ No ☐ Unk
☐ Herbal substances (please specify _____				☐ Yes ☐ No ☐ Unk
☐ Other PEGylated drug (e.g. Cimzia) (please specify _____				☐ Yes ☐ No ☐ Unk

☐ Others (please specify_____)				☐ Yes ☐ No ☐ Unk

If any other drugs were taken within 1 month of the onset, please provide a full list of these drugs, including any analgesics, general anaesthetic agents, herbal medicines and non-prescription medications.

If a printed record is available, you may provide it with this report. (If the space below is not sufficient, please continue in the space provided at the end of the report)

Name of drug/ Trade name	Total daily dose	Start date DD/MM/YY	Stop date D/MM/YY	Ongoing

Do you consider any of the concomitant drugs as a possible cause for the reported renal impairment?

Yes □ / No □

If yes, please specify which drug(s)_____

3. Laboratory data (please fill in or enclose copies of relevant lab data results) Please indicate the units used in the laboratory.

		Before Start of Drug	On daro prior to event	Date of the Renal event	Greatest Renal impairment	Period of resolution	Most recent value	
Lab Test:	**Units /Normal range**	__/__/__ **DD/MM/YY**	__/__/__ **DD/MM/YY**	__/__/__ **DD/MM/YY**	__/__/__ **DD/MM/YY**	__/__/__ **DD/MM/YY**	__/__/__ **DD/MM/ YY**	
Creatinine								
GFR								
Urea								

Potassium (K)								
Sodium (Na)								
Phosphate								
Calcium								
Albumin								
CRP								
Leukocytes								
LDH								
Urinary Analysis / Sediment: ☐ not done								
Proteinuria								☐ Yes ☐ No ☐ Unk
Hematuria								☐ Yes ☐ No ☐ Unk
Leukocyturia								☐ Yes ☐ No ☐ Unk
Erythrocytes								☐ Yes ☐ No ☐ Unk
Casts/other								☐ Yes ☐ No ☐ Unk

Other relevant Lab- Data: (e.g., antibodies, urinary or serum eosinophils etc.)

_____**Date:** __/__/__

_____**Date:** __/__/__

Please enclose also copies of all relevant information (e.g. hospital summary, results of diagnostic tests, histopathology of renal biopsy etc.).

Signature : _____ Date : _____

4. Medical History

Are any of the events/ conditions listed below known from the patient's past medical history? Yes □ / No □

If yes, please provide details below.

Pre-existing chronic kidney disease	☐ Yes Please specify suspected cause(s)	Duration	☐ No	☐ Unknown
Hypertension	☐ Yes	Duration	☐ No	☐ Unknown
Diabetes mellitus Type I or Type II if yes, please specify	☐ Yes	Duration	☐ No	☐ Unknown
Glomerulonephritis	☐ Yes, Please specify suspected cause	Duration	☐ No	☐ Unknown
Interstitial nephritis		Duration	☐ No	☐ Unknown
Pyelonephritis	☐ Yes	Number of events Number of events requiring hospitalization Date of most recent event	☐ No	☐ Unknown
Infection within the previous 30 days	☐ Yes Please specify	Treatment	☐ No	☐ Unknown

Pre-existing chronic kidney disease	☐ Yes Please specify suspected cause(s)	Duration	☐ No	☐ Unknown
Autoimmune disease	☐ Yes Please specify	Duration	☐ No	☐ Unknown
Previous treatment for a malignancy	☐ Yes Please specify	Date of Diagnosis	☐ No	☐ Unknown
Other relevant History				

5. Further information

This field provides the opportunity to provide any further information of importance in this case.

Please provide the following event details (only IF NOT PROVIDED BEFORE):

Outcome of the reported event:

Ongoing ☐ Recovered / Resolved ☐

Recovering / Resolving ☐ Not Recovered / Not Resolved ☐

Recovered with sequelae ☐ [specify: _____]

Fatal ☐ Unknown ☐

Action taken for darolutamide treatment:

Treatment discontinued permanently Yes ☐ No ☐

Treatment interrupted Yes ☐ No ☐ [If **Yes**, please provide date when treatment was restarted (if applicable): _____]

Treatment dose reduced Yes ☐ No ☐

Treatment continued without changes Yes ☐ No ☐

Causality Assessment of the event:

Related to darolutamide treatment: Yes ☐ No ☐

Please provide alternative explanation / other contributing factors: _____

Investigator's / Reporter's name..... Signature…… Date.....

Darolutamide Questionnaire
New Primary Malignancy

SECTION I - REFERENCE ID		
BAYER CASE ID:	**STUDY / PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION
REPORTER: Physician Nurse Patient Other *(specify)*:

REPORTER CONTACT INFORMATION		
Name:	**Institution/Practice Name:**	
Address:		
ZIP Code:	**City:**	**Country:**
Phone:	**Fax:**	**Email:**

PATIENT INFORMATION			
Age [years]: *(At onset of event)*	**Gender at birth:** Male Female	**Weight**	**Height**

SECTION III - PRODUCT INFORMATION Darolutamide			
Underlying malignancy /Indication:			
Dose and frequency	**Start Date** *(dd/mm/yyyy)*	**Stop date** (dd/mm/yyyy)	**Comments**

SECTION IV - ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date** (date of diagnosis) *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Outcome** *(if fatal, see Section VII)*

TREATMENT PROVIDED FOR EVENT (Please provide all anti-cancer therapies since diagnosis of the second primary malignancy)		
Treatment such as any surgery, radiation therapy, immunotherapy etc.	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*

SUSPECTED CAUSE OF EVENT

Related to Darolutamide treatment?

- ☐ Yes
- ☐ No *(specify alternative explanation/other contributing factors)*:

Alternative explanation (e.g., underlying disease / condition predisposing to the event):

Is the reported event a metastasis of the underlying prostate cancer? Yes No

Darolutamide Questionnaire
New Primary Malignancy

Action taken with Darolutamide			
Dose not changed			
Dose reduced	From:	To:	New dose:
Interrupted	From:	To:	
Drug Withdrawn	From:		
Unknown			

Did the event abate/stop after treatment stopped?	Did the event reoccur upon resuming treatment?
Yes No Unknown Not applicable	Yes No Unknown Not applicable

SECTION IV A – RELEVANT CLINICAL SYMPTOMS *(to AE of interest, which were not reported at time of first report)*

Signs or symptoms	Details *(e.g., provide values or frequency if available)*

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	Units / reference range	Before start of drug	Last values before event	After onset of event			
		Date	Date	Date	Date	Date	Date

Further investigations	Test date	Short summary of the result
Imaging study (specify technique, organ):		
Endoscopy (specify technique and body system)		
Bone marrow aspiration or biopsy Specify: _____		
Other *(specify technique, site)*:		

Darolutamide Questionnaire
New Primary Malignancy

SECTION V - RELEVANT CONCOMITANT MEDICATION						
Concomitantly administered medications given up to *1 month prior to* the reported New Primary malignancy.						
Concomitant product name	**Route of administration**	**Indication for use**	**Dose / Frequency**	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Possible cause for the event?**
						Yes No
						Yes No
						Yes No

ANTI-CANCER THERAPIES received for prostate cancer, OTHER THAN Darolutamide *If the event reported occurred during a Darolutamide clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.*				
Product name	**Start date** *(dd/mm/yyyy)*	**Duration** *[days]*	**Indication for use**	**Comment**
Hormonal therapy				
Anti-androgen				
Nilutamide				
Bicalutamide				
Flutamide				
Abiraterone				
Enzalutamide				
Apalutamide				
LHRH Agonist / Antagonist				
Goserelin				
Buserelin				
Leuprolide / Leuporelin				
Triptorelin				
Degarelix				
Other hormonal therapy specify				
Radiation Therapy				
External beam radiotherapy *site:* _____				
site: _____				
Systemic radionuclide therapy *(e.g. Lu-177-PSMA, radium-223)*				
Other *(specify:)*				

Darolutamide Questionnaire
New Primary Malignancy

ANTI-CANCER THERAPIES received for prostate cancer, OTHER THAN Darolutamide *If the event reported occurred during a Darolutamide clinical study, you do not need to enter the agents used to treat cancer as part of the study protocol.*				
Chemotherapy				
Product name	**Start date** *(dd/mm/yyyy)*	**Duration** *[days]*	**Indication for use**	**Comment**
Docetaxel				
Other *(specify)*: _____				
Other therapies				
Other *(specify)*: _____				

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history /Concurrent conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**
Smoking				
Alcohol abuse (>3 drinks/day)				
Obesity				
Exposure to ionizing radiation				
Exposure to hazardous chemicals associated to the malignancy (such as asbestos, pesticides, welding, rubber manufacturing, construction and mining)				
Chronic liver disease				
Genetic mutations (specify) _____				
History of any other cancer (besides Prostate cancer) that was diagnosed before starting Darolutamide Specify:				
Family history of cancer				
HIV infection				
Diabetes mellitus				
Other *(specify* such as heavy sunlight and UV radiation exposure etc. _____				

Darolutamide Questionnaire
New Primary Malignancy

Acute conditions *within 2 weeks* of the onset of the NEW PRIMARY MALIGNANCY				
Relevant medical history /Concurrent conditions	**Start date** *(dd/mm/yyyy)*	**On-going**	**Stop date** *(dd/mm/yyyy)*	**Details**

SECTION VII - ADDITIONAL INFORMATION / COMMENTS *(if any):*
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death *(If selected outcome was fatal)*	**Date of death** *(dd/mm/yyyy)*	**Autopsy done**	**Autopsy details** *(Continue with SECTION IV)*

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document like hospital discharge letters, histopathology report for confirmation of new malignancy diagnosis, if available.

Please sign electronically: **If your signature is not yet configured on your computer, please follow the instruction when you click in the signature field**	**Signature:**