European Union Risk Management Plan (EU-RMP)
ERLEADA® (apalutamide)

Data lock point for current RMP	13 February 2025	Version number	9.1

Date: 3 December 2025
RMP Version Number: 9.1
Supersedes Version: 8.3
EDMS Number: EDMS-RIM-1801427, 1.0

[redacted]

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	9.1
Rationale for submitting an updated RMP	To consolidate changes related to severe hepatic impairment that were submitted in working version RMP V8.2 with EMA-approved RMP V8.3.
Summary of significant changes in this RMP:	Removal of "Use in patients with severe hepatic impairment" from the list of Missing information, upon completion of the additional pharmacovigilance activity, Study 56021927PCR1026.

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	8.3
Approved within procedure	EMA/VR/0000296035
Date of approval (Competent authority opinion date)	19 November 2025 (Favorable Opinion)

TABLE OF CONTENTS

[redacted]

PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(international nonproprietary name [INN] or common name)**	Apalutamide
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Endocrine therapy, anti-androgens (L02BB05)
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ERLEADA® (further referred to as ERLEADA)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: androgen receptor (AR) antagonist
	Summary of mode of action: Apalutamide antagonizes AR signaling through inhibition of AR nuclear translocation and DNA binding to androgen response elements. Gene transcription of the androgen-driven genes, prostate-specific antigen (PSA) and transmembrane protease serine 2, is inhibited by apalutamide and results in concentration-dependent reduction of these protein levels in vitro. Apalutamide reduces proliferation of castration-resistant prostate cancer (CRPC) cells and increases apoptosis and necrosis in vivo.
	Important information about its composition: Film-coated tablets containing 60 mg or 240 mg of apalutamide
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	**Current**: Apalutamide is indicated in adult men for the treatment of non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease. Apalutamide is indicated in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).
	Proposed: Not applicable

Dosage in the EEA	**Current**: The recommended dose is 240 mg (four 60 mg tablets or one 240 mg tablet) administered as an oral single dose. The tablets should be swallowed whole and can be taken with or without food.		
	Proposed: Not applicable		
Pharmaceutical form(s) and strengths	**Current**: Slightly yellowish to greyish green, oblong-shaped, film-coated tablet, debossed with "AR 60" on one side. Each film-coated tablet contains 60 mg of apalutamide. Bluish grey to grey, oval-shaped, film-coated tablet, debossed with "E240" on one side. Each film-coated tablet contains 240 mg of apalutamide.		
	Proposed: Not applicable		
Is/will the product subject of additional monitoring in the European Union?		☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indications: non-metastatic castration-resistant prostate cancer and metastatic hormone-sensitive prostate cancer

There is limited published data specifically on NM-CRPC and mHSPC in the literature; however, data on prostate cancer (PCa), as well as data on CRPC, hormone-sensitive prostate cancer (HSPC), and metastatic disease are available, which are presented here along with any NM-CRPC- or mHSPC-specific data identified.

Incidence:

Prostate cancer is the second most common cancer among men and is the most frequently diagnosed cancer in 105 countries, with an estimated 1,276,106 new cases diagnosed in 2018 (approximately 7% of all incident cancer cases), for an age-standardized incidence risk of 29.3/100,000 population (Bray 2018).

The table below shows the estimated incidence rate of PCa in the European Union (EU) regions in 2018 (Bray 2018).

Region	Age-standardized incidence rate per 100,000 population
Northern Europe	85.7
Western Europe	75.8
Southern Europe	60.7
Eastern Europe	42.2

An observational study conducted in the United Kingdom (UK) reported that the incidence rate of CRPC was 8.3 per 100 person-years in castrated PCa patients and 3.8 per 100 person-years in all PCa patients. Mean patient age at CRPC diagnosis was 76.8 years (Hirst 2012). Specifically for NM-CRPC, a study conducted in the United States (US) in 2009 estimated the incidence of NM-CRPC to be approximately 36,100 patients per year (Scher 2015).

In the United States, the age-adjusted incidence of PCa was 109.8/100,000 men in the period between 2013 and 2017 (SEER 2020), and approximately 4.6% of patients had metastasis at diagnosis in the period between 2004 and 2012 (Bernard 2017). A US study of men diagnosed with localized PCa between 2000 and 2014 reported that 14.9% eventually developed mHSPC (Pascale 2017). A recent analysis of US SEER data showed that metastatic PCa increased significantly between 2009 and 2013, with an annual percentage change of 3.10% (Dalela 2019).

Prevalence:

In the 28 EU countries, the 5-year prevalence of PCa in 2018 was estimated to be 1,551,420 cases or 431.5/100,000 population. The estimated 5-year prevalence rate per 100,000 population in selected European countries in 2018 was as follows: France 712.0; Germany 575.3; Italy 540.9; United Kingdom 627.58; Spain 469.9; Greece 419.3; and Russian Federation 190.4 (International Agency for Research on Cancer 2018). In Nordic countries, the 10-year prevalence of PCa was

1,388/100,000 population at the end of 2016 (Engholm 2019). In the United States, the prevalence for 2015 was estimated at 1.77% of the population (Noone 2018).

In 2013, the 5-year prevalence of NM-CRPC was estimated to be 7% of all PCa patients in 5 European countries (ie, France, Germany, Italy, Spain, and the United Kingdom), based on a patient flow model. The model predicted that the 5-year prevalence of NM-CRPC will increase in the future from 89,810 patients in 2016 to 110,290 patients in 2026 (Liede 2012). In a systematic review of literature on CRPC that included a total of 71,179 patients observed for up to 12 years, 10% to 20% of PCa patients developed CRPC within 5 years of follow-up and 16% of these patients showed no evidence of bone metastasis at the time of CRPC diagnosis (Kirby 2011).

In terms of the actual number of patients, the table below shows the estimated number of mHSPC patients in 2019. Data from the following registries were used to calculate prevalence: Cancer Research UK, Institut De Veille Sanitaire, Robert Koch Institute and the Association of Population-Based Cancer Registries, the Italian Association of Cancer Registries, and the International Agency for Research in Cancer (Kantar Health 2019).

Country	Number of mHSPC patients
France	8,603
Germany	10,034
Italy	7,384
Spain	5,681
United Kingdom	11,063
United States	26,700
Japan	12,256

Demographics of the Population Within the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age:

Prostate cancer occurs primarily in older men, with the highest incidence rates in the United States being in the 70-74 age group at 673.1/100,000 population, and in the 65-69 age group at 651.7/100,000 population for the period between 2011 and 2015. There were almost no occurrences below the age of 40, and the incidence rate for the 45-49 age group for the period between 2011 and 2015 was 36.0/100,000 population (Noone 2018).

One US trial of men who developed CRPC reported that 40.6% were aged 60-69, 36.9% were aged 70-80, and 8.8% were over 80 (Shulman 2004). A study conducted in Denmark in PCa patients receiving ADT reported that, at the start of ADT, CRPC patients tended to be older (77 years) (Nguyen-Nielsen 2015). A survey of physicians conducted in France, Germany, Italy, Spain, and the United Kingdom reported that the mean age of CRPC patients was 71 years (Sternberg 2013).

Sex:

Prostate cancer affects only men.

Racial and/or ethnic origin:

The highest incidence rates of PCa were observed in Australia/New Zealand (86.4/100,000 population), Northern Europe (85.7/100,000 population), and Western Europe (75.8/100,000 population) (Bray 2018). However, the incidence of PCa varies by race and ethnicity, with black men being disproportionately affected, and black men and Caribbean men of African descent having the highest documented PCa incidence rates in the world (Bray 2018). Globally in 2018, PCa incidence rates in certain less developed regions such as the Caribbean (64.2/100,000 population), Southern Africa (64.1/100,000 population), and South America (65.9/100,000 population) were relatively high, whereas incidence rates in Asian populations remained low, estimated at 5.0/100,000 population and 10.8/100,000 population in South-Central and South-Eastern Asia, respectively.

In the United States, the incidence of PCa was 139.0/100,000 population in black males compared to 80.2/100,000 population in white males and 85.7/100,000 population for all races (Noone 2018).

Risk Factors for the Disease:

Established risk factors for PCa are advancing age and genetic factors; also a variety of environmental factors have been associated with PCa incidence and prognosis (EAU Guidelines 2021). Some research has shown that a greater basal metabolic index in PCa patients is associated with higher rates of PSA recurrence after prostatectomy (Smith 2011). Environmental factors and exogenous factors have also been found to increase risk. A diet high in red meat or high-fat dairy products, or low in fruits and vegetables may be associated with increased risk (Brawley 2012).

Main Existing Treatment Options:

Apalutamide, enzalutamide, and darolutamide with continued androgen deprivation are treatment options for patients with non-metastatic castration-resistant prostate cancer (NM-CRPC) at high risk for developing metastatic disease (European Association of Urology 2020).

The National Comprehensive Cancer Network guidelines recommend continued observation for patients with NM-CRPC with a prostate-specific antigen doubling time (PSADT) ≥10 months, as they likely have indolent disease with a lower risk of progression to metastatic castration-resistant prostate cancer (mCRPC). However, for patients with a PSADT ≤10 months, treatment is recommended, with the goal of delaying time to development of metastases (Anantharaman 2017). Although the first evidence of metastatic disease is often asymptomatic, when identified late, patients develop skeletal-related events, pain, and progressive complications that are difficult to treat (Smith 2012). Delaying of metastases for as long as possible is therefore the goal of therapy in NM-CRPC. Once the disease progresses to mCRPC, the prognosis is poor.

First-generation anti-androgens (eg, bicalutamide, nilutamide, flutamide), ketoconazole, estrogens, and corticosteroids administered in combination with ADT (eg, with gonadotropin-

releasing hormone [GnRH] agonists) have been used in the NM-CRPC setting, with no durability of response. Prior to regulatory approval of new hormonal treatments in this setting, another strategy was to switch to another anti-androgen (Luo 2016) or to withdraw anti-androgen at the time of PSA progression, which might induce a decline in PSA levels in some cases, while responses are not durable (Hong 2014).

European treatment guidelines and other expert reviews of treatment options for NM-CRPC patients both recommend apalutamide, enzalutamide, or darolutamide as the standard of care for this patient population (European Association of Urology 2021, Mateo 2019).

Treatment for mHSPC is palliative, with the goal of prolonging quantity and maintaining quality of life; with the mainstay of treatment being ADT by surgical or medical castration with a luteinizing hormone-releasing hormone agonist or GnRH antagonist. The addition of docetaxel to ADT is recommended and has been shown to improve survival (Bernard 2015). The addition of abiraterone plus prednisone to ADT has been shown to improve overall survival (Mottet 2018), while apalutamide improved radiographic progression-free and overall survival significantly when added to ADT in patients with mHSPC (Chi 2021). In addition, enzalutamide has recently been approved to treat patients with mHSPC. Current guidelines are now recommending ADT in combination with either abiraterone plus prednisone or apalutamide or enzalutamide or docetaxel in this disease setting (European Association of Urology 2021).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Prostate cancer has a variable natural history. A large proportion of all histopathological lesions currently diagnosed as PCa, progress either very slowly, or not at all, and some may even regress. For men with initially untreated PCa, the progression rate to lethal disease is 0.5% to 1.5% per year (Holmberg 2014).

Men newly diagnosed with PCa are likely to have low-grade disease which can remain indolent for more than a decade following diagnosis, with less than 6% progressing during the first 10 years of follow-up. The time between diagnosis and the appearance of clinical symptoms is estimated to be as much as 10 years for men in their 50s and 5 years for men in their 70s. However, high-grade cancers frequently progress and lead to PCa mortality within a decade (Albertsen 2015). In the United States it was estimated that among men diagnosed with PCa, 80% presented with localized disease, 12% had regional disease, and 4% had distant disease (Punnen 2013). The majority of patients with localized PCa has a 5-year survival near 100%; but once the tumor progresses, developing distant metastases, the disease often becomes incurable. The most common metastatic sites are bone and lymph nodes, but visceral metastases may also be present and may be associated with a more severe clinical course (Pascale 2017).

The prognosis for patients with CRPC is poor compared to those with HSPC (Kirby 2011). It has been reported that 33% to 46% of NM-CRPC patients develop bone metastasis within 2 years of diagnosis (Kirby 2011, Smith 2011). Median PSADT after CRPC diagnosis was 6.5 months in 1 trial of 160 patients, of whom 26.9% were metastatic at diagnosis indicating that those with a

rapidly rising PSA are at risk of developing metastatic disease (Shulman 2004). Looking at patients who received a placebo in clinical trials has shown that NM-CRPC has a median bone metastasis-free survival (MFS) of approximately 2 years (Hong 2014).

Mortality and Morbidity:

Globally, there were an estimated 358,989 deaths due to PCa in 2018, for an age-standardized risk of 7.6/100,000 population, and PCa was the fifth leading cause of death from cancer in men (Bray 2018). In Europe, the age-standardized mortality rate for PCa in 2018 was estimated at 11.3/100,000 population (International Agency for Research on Cancer 2018). In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, which was designed to evaluate the effect of screening for prostate and other cancers, the mortality rate due to PCa was 3.7/10,000 for those receiving screening and 3.4/10,000 for those receiving usual care, over a 13-year observation period (Andriole 2012).

In a UK study, mean survival duration for CRPC patients from CRPC status was 13.5 months and from first PCa diagnosis was 48.2 months (Hirst 2012). In a Swedish study of NM-CRPC patients, 64% of patients were alive 5 years after the start of ADT, and median survival was 6.5 years (Banefelt 2014).

Important Comorbidities:

Comorbidities for PCa patients on ADT include cardiovascular conditions, depression, diabetes, gastric acid disorders, hyperlipidemia, and osteoporosis (Ng 2018). Comorbidities specific to CRPC patients include hypertension, dyspnea, cardiac disease (including ischemic heart disease/angina), renal failure/impairment, diabetes mellitus, peripheral edema, hypotension, urinary disorders, anemia, digestive disorders, and respiratory infections (Hirst 2012).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings From Nonclinical Studies

The nonclinical safety profile for apalutamide has been characterized in safety pharmacology studies; genotoxicity studies; 2-year rat and 6-month transgenic mice carcinogenicity studies; single- and repeat-dose pivotal toxicology studies in rats and dogs; a fertility study in male rats; a preliminary embryo-fetal developmental toxicity study in pregnant rats; and an in vitro phototoxicity study. All in vivo toxicology studies were performed via oral (gavage) administration in rats and via capsule dosing in dogs. In support of worker safety, topically applied apalutamide was evaluated for skin sensitization potential in a murine local lymph node assay (LLNA), and ocular irritation potential in an in vitro bovine corneal opacity and permeability (BCOP) assay.

Absorption and metabolism were studied in vitro and in vivo. Distribution and excretion were studied in vivo. Protein binding and drug interaction potential were evaluated in vitro.

The nonclinical development program adhered to the requirements of the International Council for Harmonisation (ICH) guideline S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. The nonclinical safety data were extended to assess chronic toxicity, male fertility, embryo-fetal development, and carcinogenicity studies. Given the intended clinical use in adult men with NM- CRPC or mHSPC, assessment of female fertility, pre- and postnatal development, or juvenile toxicity has not been performed.

Based on the nonclinical data, the risks for nephrotoxicity, genotoxicity, and effects on the cardiovascular, respiratory and immune systems are considered limited. In general, the nature of toxicity of apalutamide was consistent with the pharmacological activity of apalutamide and comparable across species. Target organ toxicity in animals has been predictive of human toxicity, except for changes that were seen in the dog liver.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
Repeat-dose toxicology studies of 13 and 26 weeks in the rat and 13 and 39 weeks in the male dog were conducted to characterize the chronic toxicity of apalutamide when administered orally. Most toxicities observed with apalutamide in rat (at ≥25 mg/kg/day) and dog (at ≥2.5 mg/kg/day) were considered related to the pharmacological activity of the compound, and thus to interference with androgen signaling. In male animals, these effects were primarily noted in the reproductive system, including the accessory organs and mammary glands.	In general, the nature of toxicity of apalutamide was comparable across species. Target organ toxicity in animals has been predictive of human toxicity, except for changes that were seen in the dog liver. In humans, the plasma pharmacokinetics (PK) of apalutamide and its major/active metabolite N-desmethyl apalutamide were examined in 2 studies, one in subjects with pre-existing mild or moderate hepatic impairment, and the other in subjects with pre-existing severe hepatic impairment. For both studies, the comparator group was subjects with normal hepatic function. The results demonstrated that mild to moderate hepatic impairment did not influence the exposure of apalutamide and N-desmethyl apalutamide. No dose adjustment is required for patients with baseline mild or moderate hepatic impairment. In the study of subjects with severe hepatic impairment, the unbound PK parameters for apalutamide were similar following a single oral dose of 120 mg of apalutamide in subjects with severe hepatic impairment compared with a single oral dose of 240 mg of apalutamide in subjects with normal hepatic function. Per SmPC Section 4.2, the recommended dose of apalutamide is 120 mg (two 60-mg tablets) administered orally once daily for patients with severe hepatic impairment.
Associated findings included adrenocortical hypertrophy in rat and dog, and hypertrophy/hyperplasia of the pituitary gland and delayed or decreased rate of involution of the thymus in the rat. Most of the hematology changes (decrease in red blood cell mass; increase in white blood cells and platelets) as well as the increase in serum cholesterol could also be related to the mechanism of action of apalutamide. All these pharmacological effects were partially to fully reversible.	In humans, apalutamide exerts an effect of hypercholesterolemia and hypertriglyceridemia.

Key Safety Findings	Relevance to Human Usage
After chronic treatment for 39 weeks, bile duct/oval cell hyperplasia, associated with increased serum alkaline phosphatase levels, was seen in dog livers at ≥2.5 mg/kg/day. The maximum tolerated dose of apalutamide after long-term repeated dosing was 150 mg/kg/day in the rat and 10 mg/kg/day in the dog. All changes reversed or were shown to be resolving after a 4- or 8-week recovery period. Reversibility of bile duct oval cell hyperplasia in the dog was not assessed.	
Reproductive toxicity	
In repeat-dose toxicology studies in male rats and dogs, atrophy, aspermia/hypospermia, degeneration and/or hyperplasia or hypertrophy in the reproductive system were observed at doses corresponding to exposures approximately equal to the human exposure based on area under the curve (AUC). In a fertility study in male rats, a decrease in sperm concentration and motility, copulation and fertility rates (upon pairing with untreated females) along with reduced weights of the secondary sex glands and epididymis were observed following 4 weeks of dosing at doses corresponding to exposures approximately equal to the human exposure based on AUC. Effects on male rats were reversible 8 weeks after the last apalutamide administration.	Findings in the fertility study in male rats were consistent with the pharmacological activity of apalutamide (ie, AR inhibition). Male fertility in humans may be decreased by treatment with apalutamide, based on findings in repeat-dose toxicology and fertility studies which were consistent with the pharmacological activity of apalutamide. However, it is not known whether apalutamide or its metabolites are present in semen. Patients having sex with female partners of reproductive potential should use a condom along with another effective contraceptive method during treatment and for 3 months after the last dose of apalutamide.
Developmental toxicity	
In a preliminary rat study, early embryonic loss was seen at 50 and 100 mg/kg/day. In addition, a disturbance of the normal embryo-fetal development was observed ≥25 mg/kg/day (2.3 times the human exposure based on AUC), evidenced by a shortening of the mean anogenital distance, a misshapen (rounded) pituitary gland, and some skeletal variations.	Apalutamide is not indicated for use in women. Based on its mechanism of action and preliminary nonclinical data, apalutamide may cause fetal harm when administered during pregnancy.
Genotoxicity	
Apalutamide and its active metabolite N-desmethyl apalutamide were not mutagenic in either in vitro or in vivo test systems.	Apalutamide is not expected to be genotoxic in humans.

Key Safety Findings	Relevance to Human Usage
Carcinogenicity	
A 26-week carcinogenicity study was performed in the male Tg.rasH2 mouse at apalutamide dose levels of 3, 10, and 30 mg/kg/day. Apalutamide did not show evidence of a carcinogenic potential and resulted in no apalutamide-related mortality or hyperplastic and neoplastic microscopic findings. Toxicological findings were related to the pharmacological activity of apalutamide. In a 2-year carcinogenicity study in male Sprague-Dawley rats, apalutamide was administered by oral gavage at doses of 5, 15, and 50 mg/kg/day (0.2, 0.7, and 2.5 times the AUC in patients (human exposure at recommended dose of 240 mg), respectively). Neoplastic findings were noted including an increased incidence of testicular Leydig cell adenoma and carcinoma at doses greater than or equal to 5 mg/kg/day, mammary adenocarcinoma and fibroadenoma at 15 mg/kg/day or 50 mg/kg/day, and thyroid follicular cell adenoma at 50 mg/kg/day. These findings were considered rat-specific and therefore of limited relevance to humans.	The nature of toxicity of apalutamide in mice was comparable with that in repeat-dose toxicity studies in rats and dogs and was related to the pharmacological activity of apalutamide. Apalutamide was not carcinogenic in the male transgenic mouse. The increased incidence of interstitial cell adenoma and carcinoma in the testes, the adenocarcinoma and fibroadenoma in the mammary gland, and follicular cell adenoma in the thyroid gland were considered rat-specific and therefore of limited relevance for humans.
Safety pharmacology	
Cardiovascular (including potential for QT interval prolongation)	
In vitro and in vivo studies evaluated the effects of apalutamide and its metabolite N-desmethyl apalutamide on cardiovascular and respiratory systems. In vitro, apalutamide and metabolite N-desmethyl apalutamide inhibited human Ether-á-go-go Related Gene potassium current. Action potential repolarization in isolated canine Purkinje fibers was not prolonged. In telemetered dogs administered up to 40 mg/kg of apalutamide, no effects on hemodynamic and electrocardiographic parameters were recorded following a 24-hour monitoring period. Moreover, no electrocardiogram abnormalities were seen in the repeat-dose toxicology studies in dogs. A dedicated respiratory safety pharmacology study in rats did not reveal any concerns following a single dose administration of 100 mg/kg of apalutamide or metabolite N-desmethyl apalutamide.	Based on the nonclinical data, apalutamide is not expected to induce cardiovascular disorders in humans.

Key Safety Findings	Relevance to Human Usage
In these studies, apalutamide's half maximal inhibitory concentrations (IC_{50}s) and exposures covered or exceeded clinically relevant levels.	
Nervous system	
Seizures and convulsions have been observed in general toxicology studies in dogs and in non-pivotal studies in mice at high apalutamide doses and are thought to be mediated by off-target inhibition of gamma-aminobutyric acid currents ($GABA_A$) by both apalutamide and its metabolite N-desmethyl apalutamide.	Based on the nonclinical data, and as seizures have also been reported in apalutamide clinical trials, seizures are an identified risk with the use of apalutamide in humans.
The average apalutamide plasma concentration at the time of first observation of central nervous system (CNS) toxicity in dogs at 25 mg/kg/day was 30.2 µg/mL. This was about 5-fold higher than the mean apalutamide steady-state maximum plasma concentration (C_{max}) at a dose of 240 mg/day in patients with CRPC and 8-fold higher when exposure is corrected for the difference in protein binding between species. There were no CNS effects in the 13- or 39-week repeat-dose toxicology studies in male dogs at doses up to 10 mg/kg/day.	
Other	
Apalutamide and its metabolite N-desmethyl apalutamide were not phototoxic in an in vitro assay.	Based on the nonclinical data, apalutamide is not expected to be phototoxic in humans.
Based on the results of a local lymph node assay (LLNA) in the mouse, apalutamide is classified as a skin sensitizer. In the in vitro bovine corneal opacity and permeability (BCOP) assay, apalutamide did not induce ocular irritation. These studies were performed in support of worker safety (occupational toxicology).	
Nephrotoxicity	
No nephrotoxicity was identified in the clinical pathology and histopathology assessments in the 13- and 26-week rat, and 13- and 39-week dog studies.	Apalutamide is not expected to be nephrotoxic in humans.
Hepatotoxicity	
In pivotal toxicology studies in dogs, bile duct/oval cell hyperplasia and increases in serum alkaline phosphatase were observed after 39 weeks of treatment. Reversibility was not assessed.	Apalutamide may affect liver function. However, the hepatocellular hypertrophy observed in rats only was fully reversible and of no concern for humans.

Key Safety Findings	Relevance to Human Usage
Hepatocellular hypertrophy (rat only) was fully reversible.	In addition, no apalutamide-related liver function abnormalities were observed in human clinical trials.
Mechanisms for drug interactions	
In vitro, apalutamide is a substrate of cytochrome P450 (CYP)3A4 and CYP2C8 and metabolite N-desmethyl apalutamide is formed by these enzymes.	The PK of apalutamide may be affected by medications that can inhibit or induce CYP3A4 or CYP2C8. The clinical relevance of CYP3A4 and CYP2C8 in the metabolism of apalutamide was evaluated in a clinical drug-drug interaction (DDI) trial and by simulation analysis. In DDI Trial PCR1012, the C_{max} of apalutamide decreased by 21% while AUC increased by 68% following coadministration of apalutamide as a 240-mg single dose with gemfibrozil (strong CYP2C8 inhibitor). For the active moieties (sum of apalutamide plus the potency-adjusted active metabolite N-desmethyl apalutamide), C_{max} decreased by 21% while AUC increased by 45%. In Study FK10644, simulations suggest that gemfibrozil may increase the steady-state C_{max} and AUC of apalutamide by 32% and 44%, respectively. In DDI Trial PCR1012, the C_{max} of apalutamide decreased by 22% while AUC was similar following coadministration of apalutamide as a 240-mg single dose with itraconazole (strong CYP3A4 inhibitor). For the active moieties, C_{max} decreased by 22% while AUC was again similar. In Study FK10644, simulations suggest that ketoconazole (strong CYP3A4 inhibitor) may increase the steady-state C_{max} and AUC of apalutamide by 38% and 51%, respectively. The effects of CYP3A4 or CYP2C8 inducers on the PK of apalutamide have not been evaluated in vivo. Based on the DDI study results with a strong CYP3A4 inhibitor or strong CYP2C8 inhibitor, CYP3A4 or CYP2C8 inducers are not expected to have clinically relevant effects on the PK of apalutamide and the active moieties. Simulations suggest that rifampicin (strong CYP3A4 and moderate CYP2C8 inducer) may decrease the steady state C_{max} and AUC of apalutamide by 25% and 34%, respectively.

Key Safety Findings	Relevance to Human Usage
	Based upon these results, no initial dose adjustment is necessary when apalutamide is coadministered with strong inhibitors of CYP2C8 or CYP3A4, however, a reduction of the apalutamide dose based on individual tolerability should be considered. No dose adjustment is necessary when apalutamide is coadministered with inducers of CYP3A4 or CYP2C8.
Apalutamide and its N-desmethyl metabolite are inducers of human CYP2B6 and CYP3A4 in cultured hepatocytes at concentrations up to 30 μM. In vitro, apalutamide is a moderate inhibitor of human CYP isozymes CYP2C8 and CYP2B6 with IC_{50} values of 13.9 μM and 36 μM, respectively. Apalutamide is also a weak inhibitor of CYP2C9, CYP2C19, and CYP3A4 with IC_{50} values ranging from 54 μM to 67 μM. The N-desmethyl metabolite of apalutamide is a moderate CYP2B6, CYP2C8, and CYP2C9 inhibitor with IC_{50} values ranging from 38 to 49 μM in vitro. Apalutamide and its N-desmethyl metabolite do not affect CYP1A2 and CYP2D6 at therapeutically relevant concentrations.	The clinical relevance of the effect of apalutamide on substrates of CYP3A4, CYP2C9, CYP2C19, or CYP2C8 was evaluated in a clinical DDI trial PCR1020, which showed that coadministration of apalutamide with single oral doses of CYP substrates resulted in a 92% decrease in the AUC of midazolam (CYP3A4 substrate), an 85% decrease in the AUC of omeprazole (CYP2C19 substrate), a 46% decrease in the AUC of S-warfarin (CYP2C9 substrate), and an 18% decrease in the AUC of pioglitazone (CYP2C8 substrate). Based upon these results, concomitant use of apalutamide with medicinal products that are sensitive substrates of CYP3A4, CYP2C9, or CYP2C19 should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations. The effect of apalutamide on CYP2B6 substrates has not been evaluated in vivo, and the net effect is presently unknown. When substrates of CYP2B6 are administered with apalutamide, monitoring for an adverse reaction and evaluation for loss of efficacy of the substrate should be performed and dose-adjustment of the substrate may be required to maintain optimal plasma concentrations.
Based on in vitro results from transfected cell lines, apalutamide and its N-desmethyl metabolite are transporter substrates for P-glycoprotein (P-gp)/multidrug resistance protein 1 (MDR1) but not for breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP)1B1, or OATP1B3.	Because apalutamide is completely absorbed after oral administration, P-gp does not limit the absorption of apalutamide and therefore, inhibition or induction of P-gp is not expected to affect the bioavailability of apalutamide.

Key Safety Findings	Relevance to Human Usage
Apalutamide and its N-desmethyl metabolite are weak inhibitors of P-gp/MDR1, BCRP, OATP1B1, and OATP1B3 with the maximal inhibition being at most 56% at concentrations up to 30 μM. Apalutamide and its N-desmethyl metabolite were at most moderate inhibitors of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3), multidrug and toxin extrusion protein (MATE)-1, and MATE-2K. The IC_{50} towards OCT2, OAT3, and MATE-1 was calculated to be 27.2 μM, 12.0 μM, and 13.8 μM for apalutamide, respectively, and 4.8 μM, 7.6 μM, and 17.6 μM for its N-desmethyl metabolite, respectively. No in vitro inhibition by apalutamide and its N-desmethyl metabolite of OAT1 was observed.	The clinical relevance of the effect of apalutamide on substrates of P-gp and BCRP/OATP1B1 was evaluated in the DDI trial PCR1020. Apalutamide was shown to decrease the AUC of fexofenadine (P-gp substrate) by 30% and the AUC of rosuvastatin (BCRP/OATP1B1 substrate) by 41%. Based upon these results, when substrates of P-gp, BCRP, or OATP1B1 are coadministered with apalutamide, evaluation for loss of efficacy of the substrate should be performed and dose-adjustment of the substrate may be required to maintain optimal plasma concentrations. The effects of apalutamide on OCT2, MATEs, or OAT3 substrates have not been evaluated in vivo. Simulations suggest that apalutamide does not cause clinically meaningful changes in exposure to benzylpenicillin (OAT3 substrate).
Other toxicity-related information or data	
Not applicable	Not applicable

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The safety of apalutamide has been demonstrated in 4 clinical trials. In the initial Marketing Authorization Application for apalutamide, 3 clinical trials were used to support the safety of apalutamide in the NM-CRPC population: ARN-509-003 (SPARTAN), ARN-509-001, and 56021927PCR1019 (further referred to as PCR1019) (pooled safety population, N=855). To support the safety of apalutamide in the mHSPC population, additional data were presented from the clinical trial 56021927PCR3002 (TITAN) (further referred to as PCR3002) (N=524). These trials are described below.

- **Phase 3 Trial ARN-509-003** (pivotal trial) is a randomized, double-blind, multicenter trial in men with NM-CRPC. All subjects were to have a PSADT ≤10 months. Subjects were randomized in a 2:1 ratio to receive apalutamide 240 mg once daily or placebo once daily. All subjects who were not surgically castrated received ADT with a GnRH analog continuously while on study treatment.
- **Phase 1/2 Trial ARN-509-001** (supportive trial) is a 2-part, first-in-human, open-label, multicenter, proof-of-concept trial in men with progressive advanced CRPC. In Phase 1 (dose-escalation), apalutamide 30 mg to 480 mg was administered once daily to men with mCRPC. In Phase 2 (dose expansion), the recommended Phase 2 dose of 240 mg apalutamide was administered once daily to 3 cohorts of men: (1) NM-CRPC, (2) mCRPC not previously treated with abiraterone acetate (ZYTIGA®), and (3) mCRPC previously treated with ZYTIGA. All subjects who were not surgically castrated received ADT with a GnRH analog continuously while on study treatment.
- **Phase 1b Trial PCR1019** (supportive trial) is an open-label, multicenter QT/QTc (corrected for heart rate) trial in men with CRPC. Apalutamide 240 mg was administered once daily. All subjects who were not surgically castrated received ADT with a GnRH analog.
- **Phase 3 Trial PCR3002** (pivotal trial) is a randomized, double-blind, multinational, multicenter trial in men with mHSPC. Subjects were randomized in a 1:1 ratio to receive apalutamide 240 mg once daily or placebo once daily. All subjects who were not surgically castrated received ADT with a GnRH analog continuously while on study treatment.

SIII.2. Clinical Trial Exposure

The clinical development program enrolled patients with metastatic and non-metastatic progressive CRPC, and patients with mHSPC. The intended indication is for apalutamide treatment (240 mg taken orally) in the NM-CRPC population and mHSPC population. All patients are male. For the NM-CRPC population, the clinical cut-off date is based on the final analysis of data from Trial ARN-509-003 (1 February 2020). For the mHSPC population, the clinical cut-off date is based on the final analysis of data from Trial PCR3002 (07 September 2020).

Exposure in Randomized Clinical Trials

The randomized clinical trials population (N=1,327 subjects treated with apalutamide) includes 2 trials:

- Trial ARN-509-003 (N=803);
- Trial PCR3002 (N=524).

Exposure to apalutamide in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.4 for all subjects and by indication, as well as by duration, by age, by dose, and by ethnic origin, race, renal impairment at baseline and hepatic impairment at baseline.

Table SIII.1: Exposure by Duration (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Duration of exposure (months)		
0 - <4	122	257.4
4 - <8	101	583.8
8 - <12	86	876.5
12 - <16	82	1,172.6
16 - <20	55	1,006.2
20 - <24	69	1,500.6
24 - <28	55	1,437.1
28 - <32	51	1,532.6
32 - <36	57	1,923.1
≥36	649	31,432.0
Total	1,327	41,721.9
Indication: mHSPC		
Duration of exposure (months)		
0 - <4	37	80.8
4 - <8	40	241.9
8 - <12	26	266.7
12 - <16	35	496.5
16 - <20	23	420.1
20 - <24	25	543.6
24 - <28	20	518.5
28 - <32	20	596.3
32 - <36	13	442.4
≥36	285	12,700.5
Total	524	16,307.2

Table SIII.1: Exposure by Duration (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Indication: NM-CRPC		
Duration of exposure (months)		
0 - <4	85	176.7
4 - <8	61	341.9
8 - <12	60	609.8
12 - <16	47	676.1
16 - <20	32	586.1
20 - <24	44	956.9
24 - <28	35	918.7
28 - <32	31	936.3
32 - <36	44	1,480.6
≥36	364	18,731.6
Total	803	25,414.7

Trials included:
NM-CRPC: ARN-509-003.
mHSPC: PCR3002.

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Table SIII.2: Exposure by Age (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Age group (years)		
18-64	254	8,835.3
65-74	549	18,268.5
75-84	451	13,088.5
≥85	73	1,529.6
Total	1,327	41,721.9
Indication: mHSPC		
Age group (years)		
18-64	148	4,625.7
65-74	243	7,845.0
75-84	123	3,631.0
≥85	10	205.5
Total	524	16,307.2
Indication: NM-CRPC		
Age group (years)		
18-64	106	4,209.6
65-74	306	10,423.5
75-84	328	9,457.5
≥85	63	1,324.1
Total	803	25,414.7

Trials included:
NM-CRPC: ARN-509-003.
mHSPC: PCR3002.

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Table SIII.3: Exposure by Dose (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Dose of exposure		
240 mg	1,327	41,721.9
Total	1,327	41,721.9
Indication: mHSPC		
Dose of exposure		
240 mg	524	16,307.2
Total	524	16,307.2
Indication: NM-CRPC		
Dose of exposure		
240 mg	803	25,414.7
Total	803	25,414.7

Trials included:
NM-CRPC: ARN-509-003.
mHSPC: PCR3002.

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Table SIII.4: Exposure by Special Populations (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Ethnicity		
Hispanic or Latino	97	2,892.4
Not Hispanic or Latino	1,082	33,908.8
Not Reported [a]	148	4,920.7
Total	1,327	41,721.9
Race		
White	876	27,987.0
Black or African American	58	1,789.6
Asian	210	6,106.8
American Indian or Alaska Native	10	338.8
Multiple	2	90.0
Other	25	703.5
Not Reported [a]	146	4,706.2
Total	1,327	41,721.9
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	583	19,974.6
Mild (CrCl 60 to <90 mL/min)	511	15,808.2
Moderate (CrCl 30 to <60 mL/min)	213	5,425.5
Severe (CrCl <30 mL/min)	8	117.7
Missing	12	395.9
Total	1,327	41,721.9
Hepatic impairment at baseline [b]		
Normal	1,200	37,696.1
Mild	122	3,904.3
Moderate	2	24.0
Severe	0	0
Missing	3	97.5
Total	1,327	41,721.9

Table SIII.4: Exposure by Special Populations (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Indication: mHSPC		
Ethnicity		
Hispanic or Latino	86	2,659.0
Not Hispanic or Latino	426	13,244.2
Not Reported [a]	12	404.0
Total	524	16,307.2
Race		
White	354	11,125.5
Black or African American	10	338.1
Asian	118	3,667.8
American Indian or Alaska Native	6	182.1
Multiple	1	48.3
Other	24	695.7
Not Reported [a]	11	249.5
Total	524	16,307.2
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	206	6,462.6
Mild (CrCl 60 to <90 mL/min)	231	7,312.7
Moderate (CrCl 30 to <60 mL/min)	76	2,187.4
Severe (CrCl <30 mL/min)	4	99.6
Missing	7	244.9
Total	524	16,307.2
Hepatic impairment at baseline [b]		
Normal	477	15,019.6
Mild	44	1,190.0
Moderate	0	0
Severe	0	0
Missing	3	97.5
Total	524	16,307.2
Indication: NM-CRPC		
Ethnicity		
Hispanic or Latino	11	233.4
Not Hispanic or Latino	656	20,664.6
Not Reported [a]	136	4,516.7
Total	803	25,414.7
Race		
White	522	16,861.4
Black or African American	48	1,451.5
Asian	92	2,439.0
American Indian or Alaska Native	4	156.6
Multiple	1	41.7
Other	1	7.8
Not Reported [a]	135	4,456.7
Total	803	25,414.7
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	377	13,512.0
Mild (CrCl 60 to <90 mL/min)	280	8,495.5
Moderate (CrCl 30 to <60 mL/min)	137	3,238.1
Severe (CrCl <30 mL/min)	4	18.1
Missing	5	151.0
Total	803	25,414.7

Table SIII.4: Exposure by Special Populations (by Indication); Randomized Clinical Trials Population

	Patients	Person-months
Hepatic impairment at baseline [b]		
Normal	723	22,676.5
Mild	78	2,714.2
Moderate	2	24.0
Severe	0	0
Missing	0	0
Total	803	25,414.7

[a] Includes 'Unknown' and missing values.
[b] Normal (per NCI Organ Dysfunction criteria): Total bilirubin ≤ ULN and AST ≤ ULN; Mild: (Total bilirubin ≤ ULN and AST > ULN) or (ULN < Total bilirubin ≤ 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin ≤ 3 x ULN; Severe: Total bilirubin > 3 x ULN.
Keys: CrCl = creatinine clearance; ULN = upper limit normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Trials included:
NM-CRPC: ARN-509-003.
mHSPC: PCR3002.
Multiple=one or more category was selected.

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Exposure in All Clinical Trials

The all clinical trials population (N=1,379 subjects treated with apalutamide) includes 4 trials:

- 2 randomized trials ARN-509-003 (N=803) and PCR3002 (N=524);
- 2 open-label trials ARN-509-001 (N=51) and PCR1019 (N=1).

Exposure to apalutamide in the all clinical trials population is summarized in Tables SIII.5 through SIII.8 for all subjects and by indication, as well as by duration, by age, by dose, and by ethnic origin, race, renal impairment at baseline and hepatic impairment at baseline.

Table SIII.5: Exposure by Duration (by Indication); All Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Duration of exposure (months)		
0 - <4	124	258.5
4 - <8	106	613.7
8 - <12	92	936.5
12 - <16	88	1,259.7
16 - <20	56	1,024.6
20 - <24	72	1,566.7
24 - <28	61	1,595.2
28 - <32	54	1,622.0
32 - <36	60	2,023.4
≥36	666	32,489.7
Total	1,379	43,389.9
Indication: mHSPC		
Duration of exposure (months)		
0 - <4	37	80.8
4 - <8	40	241.9
8 - <12	26	266.7
12 - <16	35	496.5
16 - <20	23	420.1
20 - <24	25	543.6
24 - <28	20	518.5
28 - <32	20	596.3
32 - <36	13	442.4
≥36	285	12,700.5
Total	524	16,307.2
Indication: NM-CRPC		
Duration of exposure (months)		
0 - <4	87	177.7
4 - <8	66	371.8
8 - <12	66	669.9
12 - <16	53	763.1
16 - <20	33	604.5
20 - <24	47	1,023.1
24 - <28	41	1,076.7
28 - <32	34	1,025.7
32 - <36	47	1,580.9
≥36	381	19,789.2
Total	855	27,082.7

Trials included:
NM-CRPC: ARN-509-001, ARN-509-003 and PCR1019.
mHSPC: PCR3002.

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Table SIII.6: Exposure by Age (by Indication); All Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Age group (years)		
18-64	262	9,001.0
65-74	574	19,133.1
75-84	464	13,566.1
≥85	79	1,689.6
Total	1,379	43,389.9
Indication: mHSPC		
Age group (years)		
18-64	148	4,625.7
65-74	243	7,845.0
75-84	123	3,631.0
≥85	10	205.5
Total	524	16,307.2
Indication: NM-CRPC		
Age group (years)		
18-64	114	4,375.3
65-74	331	11,288.1
75-84	341	9,935.1
≥85	69	1,484.2
Total	855	27,082.7

Trials included:
NM-CRPC: ARN-509-001, ARN-509-003 and PCR1019.
mHSPC: PCR3002.

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Table SIII.7: Exposure by Dose (by Indication); All Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Dose of exposure		
240 mg	1,379	43,389.9
Total	1,379	43,389.9
Indication: mHSPC		
Dose of exposure		
240 mg	524	16,307.2
Total	524	16,307.2
Indication: NM-CRPC		
Dose of exposure		
240 mg	855	27,082.7
Total	855	27,082.7

Trials included:
NM-CRPC: ARN-509-001, ARN-509-003 and PCR1019.
mHSPC: PCR3002.

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Table SIII.8: Exposure by Special Populations (by Indication); All Clinical Trials Population

	Patients	Person-months
Cumulative for all indications		
Ethnicity		
Hispanic or Latino	99	2,934.2
Not Hispanic or Latino	1,132	35,535.0
Not Reported [a]	148	4,920.7
Total	1,379	43,389.9
Race		
White	924	29,560.9
Black or African American	61	1,816.4
Asian	211	6,174.0
American Indian or Alaska Native	10	338.8
Multiple	2	90.0
Other	25	703.5
Not Reported [a]	146	4,706.2
Total	1,379	43,389.9
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	605	20,670.7
Mild (CrCl 60 to <90 mL/min)	528	16,421.7
Moderate (CrCl 30 to <60 mL/min)	225	5,771.9
Severe (CrCl <30 mL/min)	8	117.7
Missing	13	408.0
Total	1,379	43,389.9
Hepatic impairment at baseline [b]		
Normal	1,248	39,208.8
Mild	125	4,047.5
Moderate	2	24.0
Severe	0	0
Missing	4	109.6
Total	1,379	43,389.9
Indication: mHSPC		
Ethnicity		
Hispanic or Latino	86	2,659.0
Not Hispanic or Latino	426	13,244.2
Not Reported [a]	12	404.0
Total	524	16,307.2
Race		
White	354	11,125.5
Black or African American	10	338.1
Asian	118	3,667.8
American Indian or Alaska Native	6	182.1
Multiple	1	48.3
Other	24	695.7
Not Reported [a]	11	249.5
Total	524	16,307.2
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	206	6,462.6
Mild (CrCl 60 to <90 mL/min)	231	7,312.7
Moderate (CrCl 30 to <60 mL/min)	76	2,187.4
Severe (CrCl <30 mL/min)	4	99.6
Missing	7	244.9
Total	524	16,307.2

Table SIII.8: Exposure by Special Populations (by Indication); All Clinical Trials Population

	Patients	Person-months
Hepatic impairment at baseline [b]		
Normal	477	15,019.6
Mild	44	1,190.0
Moderate	0	0
Severe	0	0
Missing	3	97.5
Total	524	16,307.2
Indication: NM-CRPC		
Ethnicity		
Hispanic or Latino	13	275.2
Not Hispanic or Latino	706	22,290.8
Not Reported [a]	136	4,516.7
Total	855	27,082.7
Race		
White	570	18,435.4
Black or African American	51	1,478.3
Asian	93	2,506.1
American Indian or Alaska Native	4	156.6
Multiple	1	41.7
Other	1	7.8
Not Reported [a]	135	4,456.7
Total	855	27,082.7
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	399	14,208.1
Mild (CrCl 60 to <90 mL/min)	297	9,109.0
Moderate (CrCl 30 to <60 mL/min)	149	3,584.5
Severe (CrCl <30 mL/min)	4	18.1
Missing	6	163.1
Total	855	27,082.7
Hepatic impairment at baseline [b]		
Normal	771	24,189.2
Mild	81	2,857.5
Moderate	2	24.0
Severe	0	0
Missing	1	12.1
Total	855	27,082.7

[a] Includes 'Unknown' and missing values.
[b] Normal (per NCI Organ Dysfunction criteria): Total bilirubin ≤ ULN and AST ≤ ULN; Mild: (Total bilirubin ≤ ULN and AST > ULN) or (ULN < Total bilirubin ≤ 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin ≤ 3 x ULN; Severe: Total bilirubin > 3 x ULN.
Keys: CrCl = creatinine clearance; ULN = upper limit normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Trials included:
NM-CRPC: ARN-509-001, ARN-509-003 and PCR1019.
mHSPC: PCR3002.
Multiple=one or more category was selected.
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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Use in patients with history of seizure or condition predisposing to seizure**
Reason for being an exclusion criterion	The potential mechanisms of seizures are not fully understood. Seizures/convulsions have been observed in general toxicology studies in dogs and in non-pivotal studies in mice at high apalutamide doses. Therefore, potential subjects with a history of seizure, or a condition that may have predisposed to seizure, were excluded from participation in all apalutamide clinical trials. Subjects receiving concurrent therapy with medications known to lower the seizure threshold were also excluded.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Use of apalutamide in patients with history of seizure or condition predisposing to seizure is not considered missing information since seizure is an identified risk for apalutamide. The Summary of Product Characteristics (SmPC) states that apalutamide is not recommended in patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, recent stroke (within 1 year), primary brain tumors or brain metastases. If a seizure develops during treatment with apalutamide, treatment should be discontinued permanently. The risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 2	**Patients with clinically significant cardiovascular disease**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with severe and potentially life-threatening cardiac conditions from clinical trials on anticancer therapy. Patients with clinically significant cardiovascular disease in the past 6 months were not included in the clinical development program. Clinically significant cardiovascular disease was defined as: Unstable angina, recent myocardial infarction, symptomatic congestive heart failure, recent arterial or venous thrombosis events, or clinically significant ventricular arrhythmias within 6 months prior to randomization.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Both IHD and ICVD have been added as important identified risks in the RMP, and the SmPC provides adequate guidance on the monitoring and treatment of patients with these conditions.
Criterion 3	**Medications that are strong inducers of CYP3A4 such as dexamethasone, rifampicin, rifabutin, rifapentine, carbamazepine, phenytoin, phenobarbital, efavirenz, tipranavir, or St. John's Wort**
Reason for being an exclusion criterion	In early clinical compound programs, drug interactions may be suspected to occur based on previous clinical knowledge and experience.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Drug-drug interactions were assessed by PK modeling in Study FK10644. Simulations suggest that rifampicin (strong CYP3A4 and moderate CYP2C8 inducer) may decrease the steady-state exposure of apalutamide by 25-34%. Based on the DDI study results with a strong CYP2C8 inhibitor or strong CYP3A4 inhibitor, CYP3A4 or CYP2C8 inducers are not expected to have clinically relevant effects on the PK of apalutamide and the active moieties. Therefore, no dose adjustment is necessary when apalutamide is coadministered with inducers of CYP3A4 or CYP2C8.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 4	**Potent inhibitors of CYP2C8: gemfibrozil**
Reason for being an exclusion criterion	In early clinical compound programs, drug interactions may be suspected to occur based on previous clinical knowledge and experience.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Drug-drug interactions were evaluated in Trial PCR1012 and by PK modeling in Study FK10644. Simulations suggest that gemfibrozil may increase the steady-state C_{max} and AUC of apalutamide by 32% and 44%, respectively. For the active moieties (sum of apalutamide plus the potency-adjusted active metabolite N-desmethyl apalutamide), C_{max} decreased by 21% while AUC increased by 45%. No initial dose adjustment is necessary when apalutamide is coadministered with a strong inhibitor of CYP2C8, however, a reduction of the apalutamide dose based on tolerability should be considered.
Criterion 5	**Active infection (eg, human immunodeficiency virus)**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with active infections from clinical trials on anticancer therapy. Additionally, patients with active infections may have adverse events (AEs) due to the underlying infection or may require therapy with agents that may have DDIs with the agent under study.
Considered to be included as missing information	No
Rationale (if not included as missing information)	There are no specific data available on the use of apalutamide in patients with these known active infections. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 6	**Gastrointestinal disorder affecting absorption**
Reason for being an exclusion criterion	Apalutamide is taken orally, therefore, patients needed to be able to absorb the drug that is administered orally.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Since apalutamide is administered orally, patients with gastrointestinal absorption disorders will not absorb apalutamide.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program. The intended indication is not for use in women; apalutamide is contraindicated in women who are or may become pregnant and apalutamide should not be used during breastfeeding.
Breastfeeding women	
Population with relevant different ethnic origin	The majority of apalutamide-treated subjects in clinical trials were white (Caucasian or Hispanic or Latino). Based on population PK analysis, there were no clinically relevant differences in apalutamide PK between white (Caucasian or Hispanic or Latino), black (of African heritage or African American), Asian (non-Japanese) and Japanese subjects.
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphism is not expected to affect the PK of apalutamide and N-desmethyl apalutamide.
Patients with relevant comorbidities:	
Patients with renal impairment	In the all clinical trials population, subjects with renal impairment at baseline were classified according to creatinine clearance (CrCl). Of the 1,379 subjects in the all clinical trials population, there were 528 subjects with mild renal impairment exposed for 16,421.7 person-months (CrCl 60 to <90 mL/min), 225 subjects with moderate renal impairment exposed for 5,771.9 person-months (CrCl 30 to <60 mL/min) and 8 subjects with severe renal impairment at baseline exposed for 117.7 person-months (CrCl <30 mL/min). No dedicated renal impairment study in subjects with renal impairment has been conducted. The influence of renal impairment on the exposure of apalutamide and N-desmethyl apalutamide in subjects with CRPC was investigated as part of the covariate analysis, conducted during the population PK analysis. The analysis dataset, classified according to estimated glomerular filtration rate, indicated that mild or moderate renal impairment had no statistically significant effect on systemic exposure to apalutamide and its N-desmethyl metabolite. These results support the SmPC recommendation that no dose adjustment is necessary for patients with baseline mild to moderate renal impairment.

Type of Special Population	Exposure
	No data are available in subjects with severe renal impairment. Caution is required in patients with severe renal impairment as apalutamide has not been studied in this patient population. If treatment is started, patients should be monitored for adverse reactions and if a patient experiences an adverse reaction, the dose should be reduced (SmPC).
Patients with hepatic impairment	In the all clinical trials population, subjects with hepatic impairment at baseline were classified according to the National Cancer Institute Organ Dysfunction criteria. Of the 1,379 subjects in the all clinical trials population, there were 125 subjects with mild hepatic impairment exposed for 4,047.5 person-months (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase > ULN, or ULN < total bilirubin ≤1.5 x ULN), 2 subjects with moderate hepatic impairment exposed for 24.0 person-months (1.5 x ULN < total bilirubin ≤3 x ULN) and no subjects with severe hepatic impairment at baseline (total bilirubin >3 x ULN). In a dedicated hepatic impairment study, the AUC of apalutamide and N-desmethyl apalutamide was similar in subjects with mild or moderate baseline hepatic impairment compared to subjects with normal hepatic function, with geometric mean ratios (90% confidence interval) of 94.59% (76.06, 117.64) and 113.35% (81.70, 157.26), respectively (Study 1018). These results were confirmed by the population PK analysis. No dose adjustment of apalutamide is necessary for patients with baseline mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively). In a second dedicated hepatic impairment study, the geometric mean ratio for unbound apalutamide was 103% for AUC and 78% for C_{max} in subjects with severe impairment after a single oral 120-mg dose, compared to subjects with normal hepatic function who received a single oral 240-mg dose. These results support a dose recommendation of 120 mg (two 60-mg tablets) of apalutamide administered orally once daily in patients with severe hepatic impairment (Child-Pugh Class C) (SmPC Section 4.2).
Use in patients with clinically significant cardiovascular disease defined as: Unstable angina, recent myocardial infarction, symptomatic congestive heart failure, or recent arterial or venous thrombosis events, or clinically significant ventricular arrhythmias within 6 months prior to randomization.	These patients were excluded from clinical trials. Both IHD and ICVD have been added as important identified risks in the RMP, and the SmPC provides adequate guidance on the monitoring and treatment of patients with these conditions.
Immunocompromised patients	Not applicable

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Patients with a history of seizure or condition that may predispose to seizure	Patients with a history of seizure were not included in the clinical development program. The SmPC states that apalutamide is not recommended in patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, recent stroke (within 1 year), primary brain tumors or brain metastases. If a seizure develops during treatment with apalutamide, treatment should be discontinued permanently. The risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold.

PART II: SAFETY SPECIFICATION

Module SV: Post-authorization Experience

SV.1. Post-authorization Exposure

Marketing authorization for apalutamide was granted in the European Union on 14 January 2019. Therefore, currently only worldwide post-authorization exposure data are shown.

SV.1.1. Method Used to Calculate Exposure

Product exposure is estimated at the time of distribution, not at the time of intake. A delay exists between distribution and intake.

Patient exposure has been estimated by calculation from Company distribution data. Estimates of exposure are based upon finished product, and the recommended dose of 240 mg administered once daily.

SV.1.2. Exposure

Based on the 404,346,492 units of 60 mg and 240 mg tablets distributed worldwide from launch to 31 January 2025, the estimated exposure to apalutamide is 108,848,883 person-days, or 3,628,296 person-months, or 302,358 person-years.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Apalutamide is an agent which will be prescribed under medical supervision and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

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 not Included 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):
Risk 1: Arthralgia Risk 2: Fatigue Risk 3: Skin rash[1] Risk 4: Weight decreased Risk 5: Hypercholesterolemia Risk 6: Hypertriglyceridemia Risk 7: Hypothyroidism[2] Risk 8: Pruritus
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Not applicable
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Not applicable

[1] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, and rash vesicular

[2] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased

Risks not Included in the List of Safety Concerns in the RMP
Known risks that do not impact the risk-benefit profile:
Risk 9: Drug-drug interaction (interactions with medicinal products that are substrates of CYP3A4, CYP2C9, CYP2C19, or BCRP/OATP1B1) Risk 10: Drug-drug interaction (interactions with strong inhibitors of CYP3A4 or CYP2C8)
Other reasons for considering the risks not important:
Not applicable

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Important Identified Risks	
Seizures	Seizure is an adverse drug reaction (ADR) for apalutamide, derived from nonclinical data. Seizures were observed in general toxicology studies in dogs and in non-pivotal studies in mice at high apalutamide doses and are thought to be mediated by off-target inhibition of $GABA_A$ by both apalutamide and its metabolite N-desmethyl apalutamide. Patients who had any prior history of seizure or had conditions that might predispose them to develop seizures were excluded from any apalutamide clinical trials. There were 2 events of seizure (Grade 1 and 2) reported with the use of apalutamide during clinical trials. Seizure is a serious adverse reaction that may result in persistent or significant disability and therefore, is considered an important identified risk with the use of apalutamide.
Fall	The intent-to-treat patient population are older men who are at risk for fall. During clinical trials, falls were reported in 15.6% of subjects treated with apalutamide versus 9.0% of subjects treated with placebo. Fall is an ADR associated with the use of apalutamide. Falls may result in significant disability or incapacity and therefore, is considered an important identified risk with the use of apalutamide.
Non-pathological fracture	Osteoporosis is a well-known side effect of hormone therapy for prostate carcinoma. The intent-to-treat patient population are older men who are at risk for non-pathological fractures. During clinical trials, non-pathological fractures were reported in 11.7% of subjects treated with apalutamide versus 6.5% of subjects treated with placebo. Non-pathological fractures is an ADR associated with the use of apalutamide. Non-pathological fractures may result in significant disability or incapacity and therefore, is considered an important identified risk with the use of apalutamide.

Safety Concerns for Inclusion in the RMP	Risk-benefit Impact
Missing Information	
Use in patients with severe hepatic impairment	A dedicated hepatic impairment study as well as a population PK analysis indicated that the systemic exposure of apalutamide and N-desmethyl apalutamide was similar in subjects with mild or moderate baseline hepatic impairment compared to subjects with normal hepatic function. No data are available in patients with severe hepatic impairment as these patients were excluded from the clinical development program. Therefore, and as apalutamide is primarily hepatically eliminated, apalutamide is not recommended in these patients. In addition, patients with severe hepatic impairment are not likely to benefit from apalutamide as they are more likely to die from their comorbid condition before developing PCa-related morbidity or death. Therefore, administering apalutamide would not favorably impact these patients in this setting.
Use in patients with clinically significant cardiovascular disease	Patients with clinically significant cardiovascular disease in the past 6 months were excluded from the clinical development program. There is a possibility of medical and surgical intervention so that, once stable, the patients may still benefit from apalutamide. At this time, there are no data to support the use of apalutamide in patients with clinically significant cardiovascular disease; the safety of apalutamide in these patients has not been established. If apalutamide is prescribed, patients with clinically significant cardiovascular disease should be monitored for risk factors such as hypercholesterolemia, hypertriglyceridemia, or other cardio-metabolic disorders. Patients should be treated, if appropriate, after initiating apalutamide for these conditions according to established treatment guidelines.
Carcinogenic potential	No nonclinical carcinogenicity studies have been conducted with apalutamide. Clinical studies seem to indicate that the product might increase significantly the overall survival of NM-CRPC patients with high risk for developing metastasis. In addition, ICH S1A states that in cases where the therapeutic agent is successful and life is significantly prolonged, there may be later concerns regarding second primary cancers.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

"Use in patients with severe hepatic impairment" has been removed from Missing information, upon completion of the additional pharmacovigilance activity, Study 56021927PCR1026. This study was intended to characterize this safety concern, by evaluating the pharmacokinetics of apalutamide in subjects with severe hepatic impairment compared with subjects who had normal hepatic function. Results demonstrated that a single dose of 120 mg in subjects with severe hepatic impairment is comparable to a single dose of 240 mg in subjects with normal hepatic function. No new safety signals were noted. The product label has been updated to include the 120-mg dose (two 60-mg tablets) administered orally once daily as the recommended dose for patients with severe hepatic impairment.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks:

1. Ischemic heart disease
2. Ischemic cerebrovascular disorders

There are no **important potential risks**.

Missing information:

None

Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 was used to classify the clinical trials AE information that is summarized in this Section.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk – Ischemic Heart Disease

Potential Mechanisms:

The exact mechanism is not clear. Adverse reactions associated with the use of AR inhibitors such as hypertension and dyslipidemia may contribute to the development of ischemic heart disease. In addition, ADT is a known risk factor for ischemic heart disease.

Evidence Source(s) and Strength of Evidence:

Ischemic heart disease is considered an important identified risk, based on clinical trial data in men with mHSPC (Trial PCR3002).

In Trial PCR3002 (mHSPC population), 5.9% of apalutamide-treated subjects versus 2.3% of placebo-treated subjects experienced ischemic heart disease; the exposure-adjusted incidence (events per 100 person-years) was 3.3 versus 1.6. In Trial ARN-509-003 (NM-CRPC population), ischemic heart disease was reported in 5.5% of apalutamide-treated subjects versus 2.8% of placebo-treated subjects; the exposure-adjusted incidence was numerically lower in the apalutamide arm (2.5) as compared with the placebo arm (3.6).

Ischemic heart disease is described in the current SmPC.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Ischemic Heart Disease; All Clinical Trials Population

	Randomized Trials		All Clinical Trials
	Apalutamide	Placebo/Comparator	Apalutamide
Cumulative for all indications			
Number of subjects treated	1,327	925	1,379
Frequency	75 (5.7%)	23 (2.5%)	77 (5.6%)
Seriousness			
Was serious	43 (3.2%)	13 (1.4%)	44 (3.2%)
Outcomes			
Fatal	5 (0.4%)	2 (0.2%)	5 (0.4%)
Not recovered/Not Resolved	24 (1.8%)	7 (0.8%)	25 (1.8%)
Recovering/Resolving	2 (0.2%)	2 (0.2%)	2 (0.1%)
Recovered/Resolved with sequelae	3 (0.2%)	0	4 (0.3%)
Recovered/Resolved	41 (3.1%)	12 (1.3%)	41 (3.0%)
Unknown	0	0	0
Severity (toxicity grade)			
Worst grade=1	11 (0.8%)	8 (0.9%)	12 (0.9%)
Worst grade=2	27 (2.0%)	3 (0.3%)	28 (2.0%)
Worst grade=3	20 (1.5%)	9 (1.0%)	20 (1.5%)
Worst grade=4	12 (0.9%)	1 (0.1%)	12 (0.9%)
Worst grade=5	5 (0.4%)	2 (0.2%)	5 (0.4%)
Missing grade	0	0	0
Indication: mHSPC			
Number of subjects treated	524	527	524
Frequency	31 (5.9%)	12 (2.3%)	31 (5.9%)
Seriousness			
Was serious	20 (3.8%)	5 (0.9%)	20 (3.8%)

Frequency, Seriousness, Outcomes, and Severity of Ischemic Heart Disease; All Clinical Trials Population

	Randomized Trials		All Clinical Trials
	Apalutamide	Placebo/Comparator	Apalutamide
Outcomes			
Fatal	3 (0.6%)	2 (0.4%)	3 (0.6%)
Not recovered/Not Resolved	14 (2.7%)	5 (0.9%)	14 (2.7%)
Recovering/Resolving	1 (0.2%)	0	1 (0.2%)
Recovered/Resolved with sequelae	2 (0.4%)	0	2 (0.4%)
Recovered/Resolved	11 (2.1%)	5 (0.9%)	11 (2.1%)
Unknown	0	0	0
Severity (toxicity grade)			
Worst grade=1	3 (0.6%)	6 (1.1%)	3 (0.6%)
Worst grade=2	12 (2.3%)	1 (0.2%)	12 (2.3%)
Worst grade=3	10 (1.9%)	3 (0.6%)	10 (1.9%)
Worst grade=4	3 (0.6%)	0	3 (0.6%)
Worst grade=5	3 (0.6%)	2 (0.4%)	3 (0.6%)
Missing grade	0	0	0
Indication: NM-CRPC			
Number of subjects treated	803	398	855
Frequency	44 (5.5%)	11 (2.8%)	46 (5.4%)
Seriousness			
Was serious	23 (2.9%)	8 (2.0%)	24 (2.8%)
Outcomes			
Fatal	2 (0.2%)	0	2 (0.2%)
Not recovered/Not Resolved	10 (1.2%)	2 (0.5%)	11 (1.3%)
Recovering/Resolving	1 (0.1%)	2 (0.5%)	1 (0.1%)
Recovered/Resolved with sequelae	1 (0.1%)	0	2 (0.2%)
Recovered/Resolved	30 (3.7%)	7 (1.8%)	30 (3.5%)
Unknown	0	0	0
Severity (toxicity grade)			
Worst grade=1	8 (1.0%)	2 (0.5%)	9 (1.1%)
Worst grade=2	15 (1.9%)	2 (0.5%)	16 (1.9%)
Worst grade=3	10 (1.2%)	6 (1.5%)	10 (1.2%)
Worst grade=4	9 (1.1%)	1 (0.3%)	9 (1.1%)
Worst grade=5	2 (0.2%)	0	2 (0.2%)
Missing grade	0	0	0

MedDRA terms are listed in ANNEX 7.3
Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA terms for ischemic heart disease; the subject is counted only once regardless of the number of events or the number of occurrences.
Data from the crossover period of the trial are not included.
Trials included:
NM-CRPC: ARN-509-001, ARN-509-003 and PCR1019.
mHSPC: PCR3002.
Note: Randomized trials include ARN-509-003 and PCR3002.

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Ischemic heart disease was identified as an important identified risk based on the results of Trial PCR3002 (mHSPC population) in which ischemic heart disease was reported for 5.9% of subjects treated with apalutamide and 2.3% of subjects treated with placebo; the exposure-adjusted incidence (events per 100 person-years) was 3.3 versus 1.6. For ischemic heart disease, 13 subjects in the apalutamide arm had Grade 3 or 4 events, compared with 3 subjects with Grade 3 events in the placebo arm. The following Grade 3 or 4 cardiovascular ischemic events were reported in the apalutamide arm: myocardial infarction, acute myocardial infarction, coronary artery occlusion, angina pectoris, and acute coronary syndrome. Three subjects in the apalutamide arm and 2

subjects in the placebo arm died due to ischemic heart disease. Even though the majority of subjects in Trial PCR3002 had risk factors for heart disease, the observed difference in the rate of ischemic heart disease could not sufficiently be explained by medical history. In Trial ARN-509-003 (NM-CRPC population), ischemic heart disease was reported in 5.5% of apalutamide-treated subjects versus 2.8% of placebo-treated subjects; the exposure-adjusted incidence was numerically lower in the apalutamide arm (2.5) as compared with the placebo arm (3.6). Pooled together, the overall rate of ischemic heart disease in the randomized clinical trials population was 5.7% and 2.5% for subjects treated with apalutamide or placebo, respectively. Patients with ischemic heart disease experience a high level of symptoms and symptom burden and decreased quality of life.

Risk Factors and Risk Groups:

Risk factors for ischemic heart disease include hypertension, diabetes, and dyslipidemia.

Preventability:

Subjects with clinically significant cardiovascular disease in the past 6 months were excluded from participation in all apalutamide clinical trials.

SmPC Section 4.4 states that patients should be monitored for signs and symptoms of ischemic heart disease. Management of risk factors for ischemic heart disease, such as hypertension, diabetes, or dyslipidemia, should be optimized as per standard of care.

Ischemic heart disease is listed as an ADR in the SmPC.

Impact on the Risk-benefit Balance of the Product:

Patients who had clinically significant cardiovascular disease in the past 6 months were excluded from any apalutamide trials. The observed incidence of ischemic heart disease has had a limited impact on the risk-benefit balance of the product. Whereas there is a limited impact expected in the mHSPC population, minimal impact is expected in the NM-CRPC population. The SmPC and Package Leaflet (PL) provide information to the prescriber and patient on how to manage this risk.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact of ischemic heart disease is anticipated.

Annex 1 MedDRA Term:

Ischaemic heart disease (Standardized MedDRA Query [SMQ] Broad)

Important Identified Risk – Ischemic Cerebrovascular Disorders

Potential Mechanisms:

The exact mechanism is not clear. Adverse reactions associated with the use of AR inhibitors such as hypertension and dyslipidemia may contribute to the development of ischemic cerebrovascular disorders. In addition, ADT is a known risk factor for ischemic heart as well as cerebrovascular disorders.

Evidence Source(s) and Strength of Evidence:

Ischemic cerebrovascular disorders is considered an important identified risk, based on clinical trial data in men with NM-CRPC (Trial ARN-509-003).

In Trial ARN-509-003 (NM-CRPC population), 4.0% of apalutamide-treated subjects versus 1.0% of placebo-treated subjects experienced ischemic cerebrovascular disorders; the exposure-adjusted incidence (events per 100 person-years) was 1.9 versus 0.9. In Trial PCR3002 (mHSPC population), ischemic cerebrovascular disorders occurred in 2.5% of subjects in the apalutamide group and 2.3% of subjects in the placebo group; the exposure-adjusted incidence was 1.3 for both the apalutamide arm and the placebo arm.

Ischemic cerebrovascular disorders is described in the current SmPC.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Ischemic Cerebrovascular Disorders; All Clinical Trials Population

	Randomized Trials		All Clinical Trials
	Apalutamide	Placebo/Comparator	Apalutamide
Cumulative for all indications			
Number of subjects treated	1327	925	1379
Frequency	45 (3.4%)	16 (1.7%)	47 (3.4%)
Seriousness			
Was serious	29 (2.2%)	8 (0.9%)	31 (2.2%)
Outcomes			
Fatal	3 (0.2%)	3 (0.3%)	3 (0.2%)
Not recovered/Not Resolved	13 (1.0%)	5 (0.5%)	14 (1.0%)
Recovering/Resolving	1 (0.1%)	0	1 (0.1%)
Recovered/Resolved with sequelae	6 (0.5%)	2 (0.2%)	6 (0.4%)
Recovered/Resolved	22 (1.7%)	6 (0.6%)	23 (1.7%)
Unknown	0	0	0
Severity (toxicity grade)			
Worst grade=1	14 (1.1%)	4 (0.4%)	14 (1.0%)
Worst grade=2	10 (0.8%)	4 (0.4%)	11 (0.8%)
Worst grade=3	14 (1.1%)	5 (0.5%)	15 (1.1%)
Worst grade=4	4 (0.3%)	0	4 (0.3%)
Worst grade=5	3 (0.2%)	3 (0.3%)	3 (0.2%)
Missing grade	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Ischemic Cerebrovascular Disorders; All Clinical Trials Population

	Randomized Trials		All Clinical Trials
	Apalutamide	Placebo/Comparator	Apalutamide
Indication: mHSPC			
Number of subjects treated	524	527	524
Frequency	13 (2.5%)	12 (2.3%)	13 (2.5%)
Seriousness			
Was serious	8 (1.5%)	5 (0.9%)	8 (1.5%)
Outcomes			
Fatal	2 (0.4%)	3 (0.6%)	2 (0.4%)
Not recovered/Not Resolved	7 (1.3%)	5 (0.9%)	7 (1.3%)
Recovering/Resolving	0	0	0
Recovered/Resolved with sequelae	0	1 (0.2%)	0
Recovered/Resolved	4 (0.8%)	3 (0.6%)	4 (0.8%)
Unknown	0	0	0
Severity (toxicity grade)			
Worst grade=1	4 (0.8%)	4 (0.8%)	4 (0.8%)
Worst grade=2	1 (0.2%)	3 (0.6%)	1 (0.2%)
Worst grade=3	3 (0.6%)	2 (0.4%)	3 (0.6%)
Worst grade=4	3 (0.6%)	0	3 (0.6%)
Worst grade=5	2 (0.4%)	3 (0.6%)	2 (0.4%)
Missing grade	0	0	0
Indication: NM-CRPC			
Number of subjects treated	803	398	855
Frequency	32 (4.0%)	4 (1.0%)	34 (4.0%)
Seriousness			
Was serious	21 (2.6%)	3 (0.8%)	23 (2.7%)
Outcomes			
Fatal	1 (0.1%)	0	1 (0.1%)
Not recovered/Not Resolved	6 (0.7%)	0	7 (0.8%)
Recovering/Resolving	1 (0.1%)	0	1 (0.1%)
Recovered/Resolved with sequelae	6 (0.7%)	1 (0.3%)	6 (0.7%)
Recovered/Resolved	18 (2.2%)	3 (0.8%)	19 (2.2%)
Unknown	0	0	0
Severity (toxicity grade)			
Worst grade=1	10 (1.2%)	0	10 (1.2%)
Worst grade=2	9 (1.1%)	1 (0.3%)	10 (1.2%)
Worst grade=3	11 (1.4%)	3 (0.8%)	12 (1.4%)
Worst grade=4	1 (0.1%)	0	1 (0.1%)
Worst grade=5	1 (0.1%)	0	1 (0.1%)
Missing grade	0	0	0

MedDRA terms are listed in ANNEX 7.3
Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms for ischaemic cerebrovascular disorders; the subject is counted only once regardless of the number of events or the number of occurrences.
Data from the crossover period of the trial are not included.
Trials included:
NM-CRPC: ARN-509-001, ARN-509-003 and PCR1019.
mHSPC: PCR3002.
Note: Randomized trials include ARN-509-003 and PCR3002.

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Ischemic cerebrovascular disorders was identified as an important identified risk based on the results of Trial ARN-509-003 (NM-CRPC population) in which ischemic cerebrovascular disorders were reported for 4.0% of subjects treated with apalutamide and 1.0% of subjects treated with placebo; the exposure-adjusted incidence (events per 100 person-years) was 1.9 versus 0.9.

Grade 3 events were reported for 11 subjects (1.4%) in the apalutamide arm compared with 3 subjects (0.8%) in the placebo arm; Grade 4 events were reported for 2 subjects (0.2%) in the apalutamide arm and no subjects in the placebo arm. The following Grade 3 or 4 ischemic cerebrovascular disorders were reported in the apalutamide arm: cerebrovascular accident, ischemic stroke, carotid artery stenosis, cerebral ischemia, hemiparesis, lacunar stroke, thrombotic cerebral infarction, and transient ischemic attack. Of subjects reported with a cerebrovascular event in the apalutamide arm of Trial ARN-509-003, approximately half had a history of stroke, transient ischemic attack, ischemic heart disease, or carotid artery stenosis; however, the observed difference in the rate of ischemic cerebrovascular disorders could not sufficiently be explained by medical history.

In Trial PCR3002 (mHSPC population), ischemic cerebrovascular disorders were reported for 2.5% of subjects in the apalutamide group and 2.3% of subjects in the placebo group; the exposure-adjusted incidence was numerically the same for the apalutamide (1.3) and placebo (1.3) arms. Pooled together, the overall rate of ischemic cerebrovascular disorders in the randomized clinical trials population was 3.4% and 1.7% for subjects treated with apalutamide and placebo, respectively.

Risk Factors and Risk Groups:

Risk factors for ischemic cerebrovascular disorders include hypertension, diabetes, and dyslipidemia.

Preventability:

SmPC Section 4.4 states that patients should be monitored for signs and symptoms of ischemic cerebrovascular disorders. Management of risk factors for ischemic cerebrovascular disorders, such as hypertension, diabetes, or dyslipidemia, should be optimized as per standard of care.

Ischemic cerebrovascular disorders is listed as an ADR in the SmPC.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of ischemic cerebrovascular disorders has had a limited impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage this risk.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact of ischemic cerebrovascular disorders is anticipated.

Annex 1 MedDRA Term:

Ischaemic central nervous system vascular conditions (SMQ)

SVII.3.2. Presentation of the Missing Information

Not applicable

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Ischemic heart disease Ischemic cerebrovascular disorders
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Post-Authorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns		
Safety Concern	Purpose/Description	
Not applicable		
Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Post-Authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Ischemic heart disease	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation to monitor for signs and symptoms of ischemic heart disease is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic heart disease is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of heart disease is provided in PL Section 2 and PL Section 4 **Other routine risk minimization measures beyond the Product Information:** • Legal status
Ischemic cerebrovascular disorders	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation to monitor for signs and symptoms of ischemic cerebrovascular disorders is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic cerebrovascular disorders is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of stroke or mini- stroke is provided in PL Section 2 and PL Section 4

Safety Concern	Routine Risk Minimization Activities
	Other routine risk minimization measures beyond the Product Information: • Legal status

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Additional Risk Minimization

Not applicable

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Ischemic heart disease	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic heart disease is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic heart disease is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of heart disease is provided in PL Section 2 and PL Section 4 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Ischemic cerebrovascular disorders	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic cerebrovascular disorders is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic cerebrovascular disorders is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of stroke or mini-stroke is provided in PL Section 2 and PL Section 4 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for ERLEADA (Apalutamide)

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

ERLEADA's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how ERLEADA should be used.

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

I. The Medicine and What it is Used For

ERLEADA is authorized for the treatment of non-metastatic castration-resistant prostate cancer (NM-CRPC) in adult men who are at high risk of developing metastatic disease and for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see SmPC for the full indication). It contains apalutamide as the active substance and it is given as an oral tablet.

Further information about the evaluation of ERLEADA's benefits can be found in ERLEADA'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/erleada.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

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

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

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and analyzed regularly, 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.

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

II.A. List of Important Risks and Missing Information

Important risks of ERLEADA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ERLEADA. 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 (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Ischemic heart disease Ischemic cerebrovascular disorders
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Ischemic heart disease	
Evidence for linking the risk to the medicine	Ischemic heart disease is considered an important identified risk, based on clinical trial data in men with mHSPC (Trial PCR3002). In Trial PCR3002 (mHSPC population), 5.9% of apalutamide-treated subjects versus 2.3% of placebo-treated subjects experienced ischemic heart disease; the exposure-adjusted incidence (events per 100 person-years) was 3.3 versus 1.6. In Trial ARN-509-003 (NM-CRPC population), ischemic heart disease was reported in 5.5% of apalutamide-treated subjects versus 2.8% of placebo-treated subjects; the exposure-adjusted incidence was numerically lower in the apalutamide arm (2.5) as compared with the placebo arm (3.6). Ischemic heart disease is described in the current SmPC for ERLEADA.
Risk factors and risk groups	Risk factors for ischemic heart disease include hypertension, diabetes, and dyslipidemia.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic heart disease is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic heart disease is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of heart disease is provided in PL Section 2 and PL Section 4 • Legal status Additional risk minimization measures: • None
Important Identified Risk: Ischemic cerebrovascular disorders	
Evidence for linking the risk to the medicine	Ischemic cerebrovascular disorders is considered an important identified risk based on clinical trial data in men with NM-CRPC (Trial ARN-509-003). In Trial ARN-509-003 (NM-CRPC population), 4.0% of apalutamide-treated subjects versus 1.0% of placebo-treated subjects experienced ischemic cerebrovascular disorders; the exposure-adjusted incidence (events per 100 person-years) was 1.9 versus 0.9. In Trial PCR3002 (mHSPC population), ischemic cerebrovascular disorders were reported for 2.5% of subjects in the apalutamide group and 2.3% of subjects in the placebo group; the

	exposure-adjusted incidence was numerically the same for the apalutamide (1.3) and the placebo (1.3) arms. Ischemic cerebrovascular disorders is described in the current SmPC for ERLEADA.
Risk factors and risk groups	Risk factors for cerebrovascular disorders include hypertension, diabetes, and dyslipidemia.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic cerebrovascular disorders is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for cerebrovascular disorders is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of stroke or mini-stroke is provided in PL Section 2 and PL Section 4 • Legal status Additional risk minimization measures: • None

II.C. Post-authorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

Not applicable.

II.C.2. Other Studies in Post-authorization Development Plan

Not applicable

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not Applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable