15 November 2018
EMA/879617/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Erleada

International non-proprietary name: apalutamide

Procedure No. EMEA/H/C/004452/0000

Note

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

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Administrative information

Name of the medicinal product:	Erleada
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	apalutamide
International Non-proprietary Name:	apalutamide
Pharmaco-therapeutic group (ATC Code):	Endocrine therapy, anti-androgens ATC code: L02BB05
Therapeutic indication(s):	Erleada 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 (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	60 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PCTFE/alu) and bottle (HDPE)
Package size(s):	Blister: 112 tablets and 120 tablets Bottle: 120 tablets

Table of contents

List of abbreviations

ADR	adverse drug reaction
ADT	androgen deprivation therapy
AR	androgen receptor
ARV7	androgen receptor splice variant 7
AUC	area under the plasma concentration-time curve
BCS	biopharmaceutical classification system
BICR	blinded independent central review
BCRP	breast cancer resistance protein
BSA	body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent oral clearance
Cmax	maximum observed plasma concentration
Cmin	minimum observed plasma concentration
CQA	critical quality attributes
CPP	critical process parameters
CRPC	castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DAD	diode array detector
DSC	differential scanning calorimetry
DVS	dynamic vapour sorption
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FACT-P	Functional Assessment of Cancer Therapy–Prostate
FC	film-coated
FDA	Food and Drug Administration

GC-FID Gas chromatography flame ionization detector

GMR geometric mean ratio

GnRHa gonadotropin-releasing hormone agonist

HDPE High-density polypropylene

HPMC-AS Hydroxypropyl methylcellulose acetate succinate polymer

HR hazard ratio

ICH International Conference on Harmonisation

IDMC Independent Data Monitoring Committee

INN International non-proprietary name

IR infrared spectroscopy

ITT Intent-to-treat

LDPE Low-Density Polyethylene

LF liquid-filled

LOQ limit of quantification

MATE multidrug and toxin extrusion

mCRPC metastatic castration-resistant prostate cancer

MTDSC modulated temperature differential scanning calorimetry

MFS Metastasis free survival

NCCN National Comprehensive Cancer Network

NCI CTCAE National Cancer Institute Common Toxicity Criteria for Adverse Events

NIR Near infrared

NMR nuclear magnetic resonance

OATP organic anion transporting polypeptide

OBF O'Brien-Fleming

OCT2 organic cation transporter 2

OS overall survival

PAR Proven Acceptable Range

PP Polypropylene

PVC-PCTFE Polyvinyl Chloride-Polychlorotrifluoroethylene

PFS Progression free survival

PFS2 Progression-free Survival During First Subsequent Therapy

P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PRO	patient-reported outcome
PSA	prostate specific antigen
PSADT	PSA doubling time
PTR	peak-to-trough
PXR	pregnane X receptor
P-Y	patient-years
QC	Quality control
QTPP	Quality Target Product Profile
RH	relative humidity
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SLS	Sodium Lauryl Sulfate
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TGA	thermogravimetric analysis
tmax	median time to achieve peak plasma concentration
TSH	thyroid-stimulating hormone
TTC	threshold of toxicological concern
TTM	time to metastasis
UGT	UDP-glucuronosyl transferase
UHPLC	Ultra high pressure liquid chromatography
US	United States
UV	Ultraviolet
VAS	visual analogue scale
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 8 February 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Erleada, through the centralised procedure falling within the Article 3(1) and point 3. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2016.

The applicant applied for the following indication

Erleada is indicated for the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 (EMEA-36-2014) on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance apalutamide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received scientific advice from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2344/1/2012/SME/III	21 June 2012	of dossier the sci adv pertained to non-clinical and clinical
EMEA/H/SA/2344/1/FU/1/2013/II	19 December 2013	of dossier the sci adv pertained to clinical
EMEA/H/SA/2344/2/2014/I	20 February 2014	of dossier the sci adv pertained to quality
EMEA/H/SAH/027/1/2014/II	25 September 2014	of dossier the sci adv pertained to clinical
EMEA/H/SA/2344/3/2014/III	26 September 2014	of dossier the sci adv pertained to quality, non-clinical & clinical
EMEA/H/SAH/031/1/2014/II	26 February 2015	of dossier the sci adv pertained to clinical
EMEA/H/SAH/031/2/2015	21 May 2015	of dossier the sci adv pertained to clinical
EMEA/H/SA/2344/2/FU/1/2016/I	10 November 2016	of dossier the sci adv pertained to quality
EMEA/H/SA/2344/2/FU/2/2017/I	23 March 2017	of dossier the sci adv pertained to quality
EMEA/H/SAH/031/3/2017/II	22 June 2017	of dossier the sci adv pertained to clinical

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Natalja Karpova

The application was received by the EMA on	8 February 2018
The procedure started on	1 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	31 May 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	30 May 2018

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	8 June 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 June 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 July 2018
The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: - A GCP inspection at 4 sites (CRO, two clinical investigator sites and one technical facility) in US, New Zealand and Taiwan between June and September 2018. The outcome of the inspection carried out was issued on	15 October 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	5 September 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 September 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	20 September 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 October 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	31 October 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 November 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Erleada on	15 November 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Apalutamide is intended for the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease.

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

2.1.2. Epidemiology

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

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

2.1.3. Clinical presentation, diagnosis and stage / prognosis

Non-metastatic castration-resistant prostate cancer represents a spectrum of disease with risk for development of metastases, particularly for those patients with a PSADT ≤10 months. It is also defined by a castration level of serum testosterone (ie, <50 ng/dL), rising PSA, and no evidence of metastatic disease.

Men with a PSADT of ≤10 months are at the highest risk for developing imminent metastatic disease and prostate cancer-specific death. Androgen-receptor signaling remains active even with castration levels of serum testosterone. Molecular profiling studies of CRPC commonly show increased AR gene expression. This underscores the emerging view that current androgen-depletion strategies are incomplete, and that residual androgen contributes to sustained AR activity and disease progression.

For patients with PSADT nearing 10 months and whose PSA kinetics are accelerating, the window of opportunity to prevent metastases is small and could be missed. Moreover, current treatment guidelines do not offer recommendations for PSA testing.

2.1.4. Management

Currently, patients with non-metastatic prostate cancer who have rising prostate specific antigen (PSA) levels despite definitive and salvage local therapy are frequently treated with either medical or surgical castration therapy, aimed at blocking AR signalling. Patients initially benefit from androgen deprivation therapy (ADT) but the disease eventually progresses after approximately 12 to 48 months. Resistance to ADT is largely driven by reactivation of AR signalling through persistent adrenal androgen production, up-regulation of intratumoural testosterone production, modification of the biologic characteristics of ARs, and steroidogenic parallel pathways.

Although high-risk non-metastatic CRPC (i.e., for patients with a short PSA doubling time) is a disease state, current treatment options are limited. Per a provisional opinion from the American Society of Clinical Oncology (ASCO), second-line hormonal therapy (e.g., antiandrogens, cytochrome P450 [CYP] 17 inhibitors) may be considered in patients with nonmetastatic CRPC at high risk for metastatic disease (based on a short PSA doubling time or rapid velocity), but otherwise this treatment is not suggested [Virgo et al, 2017]. Similarly, the National Comprehensive Cancer Network (NCCN) guideline recommends first-generation antiandrogens (e.g.,

bicalutamide, nilutamide, flutamide), second-generation novel hormonal therapies (enzalutamide, abiraterone), ketoconazole, corticosteroids or diethylstilbestrol as second-line hormonal therapies [NCCN, 2017]. The European Society for Medical Oncology guidelines advise ADT and watchful waiting [Parker et al, 2015].

About the product

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the lack of maturity of long-term variables including Overall Survival and the absence of a beneficial effect on Quality of Life that cannot substantiate the claim that apalutamide addresses to a significant extent an unmet medical need and that it is of major public health interest.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 60 mg of apalutamide as the active substance.

The finished product is an immediate release, oblong shaped, greenish film-coated tablet of 16.7 mm length, debossed with "AR 60" on one side.

Other ingredients, as described in section 6.1 of the SmPC, are:

Tablet core: colloidal anhydrous silica, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, microcrystalline cellulose (silicified),

Film-coating: iron oxide black (E 172), iron oxide yellow (E 172), macrogol, poly(vinylalcohol) (partially hydrolyzed), talc, titanium dioxide (E 171).

The product is available in a white opaque high density polypropylene (HDPE) bottle with a polypropylene (PP) child resistant closure and silica gel desiccant or opaque polyvinyl chloride-polychlorotrifluoroethylene (PVC-PCTFE) foil blister with an aluminum push-through foil sealed inside a wallet pack, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of apalutamide is 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-thioxo-5, 7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide, corresponding to the molecular formula $C_{21}H_{15}F_4N_5O_2S$. It has a relative molecular mass 477.43 g/mol and has the structure shown in *Figure 1*.

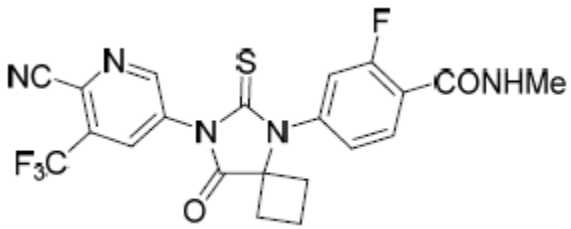


Figure 1. Chemical structure of apalutamide.

Apalutamide appears as white to slightly yellow non-hygroscopic crystalline powder. It is practically insoluble in aqueous media over a wide range of pH values. Its pKa was determined to be 9.7 (acidic carboxamide moiety) and its partition coefficient (Log P) is 2.89 (pH 7.0).

The structure of the active substance was elucidated by a combination of spectroscopic methods (UV, IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry), elemental analysis, DSC and TGA. Apalutamide is sufficiently characterised and its structure is adequately elucidated.

Apalutamide is an achiral molecule. It exhibits polymorphism, with Form B being the thermodynamically most stable form of apalutamide under the relevant crystallization and storage conditions of the active substance. The active substance synthesis process was designed to consistently deliver Form B.

Manufacture, characterisation and process controls

Apalutamide is manufactured through a five step synthesis reaction and purification process. The choice of the starting materials (SMs) is in line with previous CHMP Scientific Advice and the justification for all three was provided in accordance to ICH Q11. They were therefore considered acceptable and are controlled by appropriate specifications.

The intermediates are controlled by appropriate specifications. The applicant has performed a criticality assessment of quality attributes. It was done in order to determine the critical quality attributes (CQA). All CQAs have been selected and justified taking into account the quality target product profile (QTPP). Critical steps and process parameters have been identified and for all critical process parameters (CPPs), proven acceptable ranges (PARs) were established. Overall the control strategy is satisfactory and ensures the consistent quality of the final active substance. The characterisation of the active substance and its impurities are in accordance with the relevant ICH guidelines. Detailed information on the origin, fate, and control of the actual synthesis and carryover impurities was provided. Carry-over studies of potential impurities coming from starting material to the final active substance were conducted. Taking into consideration the above, the conclusion is that the manufacturing process is capable to remove these impurities. Solvents which are used in the last step of the synthesis, are controlled in the active substance specification.

The mutagenicity assessment showed that two impurities belong to the ICH M7 class 3. For both impurities it has been shown that they are satisfactorily controlled.

Two solvents are known carcinogenic or mutagenic compounds, but based on purging factor considerations under the applicable process conditions they are not expected to occur in the final active substance at levels above their acceptable limits, and therefore do not require specific control actions.

Two different synthetic routes were used during process development: synthesis method 1 and synthesis method 2. The synthesis method 1 was not a commercially viable route; therefore synthesis method 2 was developed. Three different versions of synthesis method 2 were developed. The commercial route of apalutamide active substance is clearly defined. Differences between the different versions of synthesis methods were discussed and justified.

Apalutamide active substance is packaged in double, antistatic, low-density polyethylene (LDPE) bags, which are closed appropriately with a twist-tie or equivalent. The bags are placed in a closed container (plastic drum, fiber drum, or equivalent). The container closure system intended for commercial packaging of the active substance complies with the current European guideline on Plastic Immediate Packaging Materials CPMP/QWP/4359/03, including Regulation (EU) No 10/2011 on Plastic Materials and Articles Intended to Come into Contact with Food. The packaging material is controlled by acceptable in house specification. The suitability of this container closure system is demonstrated by the active substance stability data.

Specification

The active substance specifications reproduced include appropriate tests and limits for appearance (visual), identification (IR), assay (UHPLC-DAD), chromatographic purity (UHPLC-DAD), residual solvents (GC-FID) and sulphated ash (USP).

The specifications for release and stability testing of the active substance have been established in accordance with ICH Q6A. The justifications for the selection of the specification parameters, the selection of the test methods and the setting of the acceptance criteria are based on relevant development data, pharmacopoeial standards, test results from representative active substances batches generated with the proposed test methods and results from long-term and accelerated stability studies. Additionally, a reasonable range of expected analytical and manufacturing variability is considered, taking into account the limited amount of data available to date. The proposed levels for the impurities are considered adequate and have been qualified by relevant toxicological studies.

Rationale for the absence of particle size specification was considered justified.
A risk assessment for the potential presence of elemental impurities in the active substance was conducted in accordance with the ICH Q3D, taking into account potential contributions from manufacturing equipment, container closure system (primary packaging), processing water and elements intentionally added during the synthesis process. Based on the outcome of the risk assessment and the results of three representative commercial scale apalutamide batches it was shown that all elements are well below 30% of the ICH Q3D option 1, and therefore no testing for elemental impurities has been included in the active substance specification.

Based on the available development data and the general nature of the synthetic process employed the routine microbial purity testing of the active substance is considered not necessary and therefore no test for microbial purity is included in the specification.

The analytical methods used for the control of the active substance are adequately described and non-pharmacopoeial methods have been validated. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch results were presented for 13 batches manufactured during the course of development, by the proposed commercial process. All batches meet the proposed commercial specifications. Results for batches

manufactured by the other processes were also presented. In all cases, the batches comply with the specification proposed at the time of release.

Stability

Stability data from three production scale batches stored in the intended commercial packaging for up to 18 months under long term conditions (25 °C / 60% RH and 30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) was provided according to the ICH guidelines.

In addition, long term stability data for up to 24 months on another three production scale batches manufactured at the synthesis development site using a previous synthesis method, which however is representative for the final commercial method, were also presented.

As the available long term stability data on commercial batches does not cover the proposed re-test period at the time of approval, the applicant commits to continue the stability studies post-approval for the active substances batches under long-term storage conditions 25 °C/60% RH and 30 °C/75% RH, in accordance to the protocols presented in 3.2.S.7.1.

The following parameters were tested in stability studies: appearance, assay, chromatographic purity, water content and solid state. Microbiological purity was tested at the beginning of long term study and once a year at 25°C/60%RH and, once a year at 30°C/75%RH. The test methods used for stability testing are the same as the proposed commercial test methods. The following test methods: water content by Karl Fischer, solid state by XRD, and microbiological purity (Ph. Eur. 2.6.12) are only used for the stability studies. Method description and validation reports for the water content method and method description report for the solid state method are provided. The test results for all batches, in all storage conditions and time points comply with the proposed specifications and no significant stability related changes or trends have been observed for any of the tested parameters. The polymorphic form of the apalutamide active substance is maintained during storage.

Photostability was investigated according to ICH Q1B. Both protected and unprotected samples were stable when exposed to light. Nevertheless, the applicant wishes to apply the storage condition “store in original package to protect from light” as a precaution measure. As there is no impact to the end user of the finished product neither to the pharmaceutical distribution chain, no objection is raised and the proposed storage condition is accepted.

Forced degradation studies on the active substance in solution under stress conditions of thermal acidic, thermal alkaline, thermal oxidative, neutral, dry heat, humid heat, and metal ions were performed. Results from the forced degradation studies including assay and chromatographic purity results and mass balance calculations in the form of table were presented. The active substance was found stable under neutral conditions and when exposed to metal ions. Apalutamide is prone to minor degradation under strong acidic and thermal conditions and unstable under alkaline and strong oxidative conditions. The primary degradation process of the active substance was described and the stability indicating nature of the UHPLC method for related substance and assay was shown.

Based on the available stability data a retest period of 30 months is accepted. The storage labelling should state “Store in original package” to protect from light. The active substance does not require any special temperature storage conditions.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Erleada is an immediate release, oblong shaped, greenish film-coated tablet of 16.7 mm length, debossed with "AR 60" on one side. Each film-coated tablet contains 60 mg of apalutamide.

The Quality Target Product Profile (QTPP) for Erleada was defined as an immediate-release, oral, film-coated tablet, containing minimum 60 mg of apalutamide for dosing a maximum of 4 tablets a day, enabling a daily dose of 240 mg; the finished product must have a sufficiently low level of impurities and microbial burden, with a shelf life of minimum 24 months when packaged in blisters or bottles and stored at room temperature.

Based on the low aqueous solubility observed across the studied pH range, and high intestinal permeability, the active substance is a class 2 compound according to the biopharmaceutical classification system (BCS) for the maximum dose of 240 mg per intake as per the SmPC. The low solubility of active substance (AS) in aqueous media was the main challenge of formulation development. In order to improve the bioavailability of this BCS Class 2 substance in Erleada, development focused on increasing the active substance's aqueous solubility and dissolution rate.

Development work started with a different pharmaceutical form and strength. Further investigations were made towards a more stable formulation of higher dosage strength. To manage the low aqueous solubility of apalutamide, enabling technologies were explored. Selected formulations of film-coated tablets were optimised. Several human bioavailability studies were performed to compare pharmacokinetic parameters.

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The excipients are well known, conventional excipients for use in film-coated tablets. The active substance compatibility with the excipient used for the intermediate as studied and demonstrated under conditions relevant for the manufacturing of the intermediate. Compatibility with other excipients was demonstrated within stability studies of the finished product.

Ensuring and maintaining the solid state of the intermediate is important for the bioavailability of the product. Therefore, the solid state of the intermediate has been monitored extensively at release and during stability studies of the intermediate and of the finished product throughout development. The solid state of apalutamide in the intermediate was characterised on representative batches manufactured by the development site as well as the commercial site. Different techniques, including powder X-ray diffraction (XRD), infrared spectroscopy (IR), modulated temperature differential scanning calorimetry (MTDSC), dynamic vapour sorption (DVS) and near infrared spectroscopy (NIR), were used. Data was also collected during storage at 25 °C/60% RH, 30 °C/75% RH, and 40 °C/75% RH when packaged in the proposed container closure system (low-density polyethylene bag in an aluminum laminated bag). All available data show that the intermediate is stable during storage of the intermediate and during the manufacture and storage of the finished product in the proposed container closure system.

It has been demonstrated that the particle size distribution of the active substance does not impact the manufacturability, quality, or performance of the finished product and that the particle size range studied of the intermediate does not have an impact on the *in vivo* performance of the finished product.

The development of the dissolution method was described sufficiently and was subject of Scientific Advice given by CHMP. The proposed dissolution method has been optimised for the following parameters: medium pH, type of surfactant and its concentration in the medium and the paddle rotation speed. The developed dissolution method has demonstrated to be able to provide discriminating capabilities towards certain material attributes

and process parameters and storage. Considering the provided information, the CHMP agreed that the proposed dissolution method is suitable for the routine quality control of Erleada finished product.

The manufacturing process development was based on science-based criticality analysis approach that was performed to determine the manufacturing process steps and parameters that could influence quality attributes of finished product. This approach assigns criticality based on process parameter and material attribute impact on the finished product Critical Quality Attributes (CQAs). The CQAs are derived from the QTPP and patient impact (safety, efficacy, and therapy compliance). A comprehensive criticality analysis was conducted to determine an appropriate control strategy for the drug product CQAs. Based on the development knowledge and using quality risk management tools as described in ICH Guideline Q9, the drug product manufacturing process was systematically evaluated to determine which process parameters and material attributes can potentially impact the CQAs of the finished product. The criticality of the process parameters and material attributes were assigned based on their impact on the finished product CQAs within potential operating ranges. The identified critical process parameters (CPPs), critical material attributes of active substances or excipients (CMAs), and critical attributes of finished product intermediates (CINT) were evaluated against the risk of CQA failure. Based on the outcome of this evaluation, a risk-based control strategy was proposed.

Process parameters and their proven acceptable ranges were selected based on identified risks. The ranges were developed and studied at both pilot and commercial scaled batches. Successful transfer from development sites to commercial manufacturing sites, as well scale-up from pilot to commercial batch sizes were performed. The only difference between the commercial tablets and the tablets used in the primary stability studies and pivotal clinical phase 3 trial is a debossment. In order to demonstrate equivalency in the quality and performance of the clinical phase 3 batches with the primary stability and commercial site batches, an *in vivo* and an *in vitro* comparison have been performed.

The finished product is packaged in bottle or blisters. The blisters are made of opaque polyvinyl chloride-polychlorotrifluoroethylene (PVC-PCTFE) foil blister with an aluminium (Alu) push-through foil. The bottles are white, opaque, 160-mL high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closure and induction seal liner containing silica gel desiccant (6 g silicon dioxide in total).

The selected container closure systems for the finished product as well as for the intermediate (LDPE in Alu laminated Bag) comply with the relevant Regulation (EU) No 10/2011 on Plastic Materials and Articles Intended to Come into Contact with Food and European guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03).

Manufacture of the product and process controls

Erleada film coated tablets manufacturing process of the finished product is a multistep process comprising preparation of intermediate, pre-blending, granulation, post granulation blending and lubrication, film-coating and packaging.

The critical controls for the finished product manufacturing process have been determined using a science-based criticality analysis approach. The approach assigned criticality based on process parameter and material attribute impact on critical quality attributes (CQAs). Assessment of the criticality of process parameters identified two critical steps. Although no impact of the manufacturing process parameters on the CQAs of the finished product has been observed within the studied ranges, the process parameters related to the manufacture of the intermediate are designated as CPPs as they can affect stability and dissolution.

The manufacturing process contains one drug product intermediate for which the specification was provided and justified. NIR test methods will be used to determine water content and solid state of the active substance in the intermediate. A stability study of the intermediate demonstrated that no changes in appearance, assay, degradation products, water content, solid state by XRD is observed over a period of 12 months. Stability data of two bulk film-coated batches have also been submitted. These data support the proposed 12 months hold time for bulk film-coated tablets packaged in a closed low density polyethylene (LDPE) bag in a heat-sealed aluminium (Alu) laminated bag placed in a closed container (plastic drum, fibre drum or equivalent).

The manufacturing process has been validated on three batches of film coated tablets at commercial scale. The intermediate manufacturing process was also validated in three consecutive validation batches for the intended commercial batch sizes. All validation data generated met the acceptance criteria and confirm that the process is well controlled and that product of consistent quality is manufactured.

Product specification

The finished product release and shelf life specifications include appropriate tests and acceptance criteria for this product type; description (appearance and tablet dimension, visual and measurement, respectively), identification (UHPLC, UV), assay (UHPLC), chromatographic purity (UHPLC), uniformity of dosage forms (UHPLC), dissolution, water content (Karl-Fischer, NIR), solid state (NIR) and microbial purity (Ph. Eur.).

The specifications for release and stability testing have been established in accordance with ICH Q6A.

The justifications are based on relevant development data, pharmacopoeial standards, test results from representative finished product batches generated with the proposed test methods and results from long-term and accelerated stability studies. Additionally, when setting the specifications, a reasonable range of accepted analytical and manufacturing variability was also factored in, taking into account the limited amount of data available to date.

Characterization, mutagenicity, and toxicological qualification information for the specified degradation product and synthesis impurity has been presented. No other actual degradation products have been observed at or above the ICH Q3B reporting threshold of 0.1% (maximum daily dose of apalutamide is 240 mg) during release or long-term stability testing of the finished product packaged in the proposed container closure system. No potential degradation products have been observed at or above the ICH Q3B identification threshold of 0.2% during accelerated stability studies (40 °C/75% RH) or confirmatory photostability studies. Therefore, in alignment with ICH Q3B and ICH M7, no additional toxicological qualifications and mutagenic assessments are required.

A test for solid state by NIR spectroscopy is included in the finished product specification. The limit proposed for this parameter, at release and shelf-life, is supported by the batch analysis results and by the stability data. NIR spectroscopy is also used to determine water content in the finished product. Changes outside of the approved scope (solid state and water content) of the NIR procedures are subject to variation application.

A risk-based assessment was conducted in accordance with ICH Q3D, taking into account any potential contributions from the active substance, excipients, manufacturing equipment and container closure system into the finished product. Based on this assessment, testing of the finished product for elemental impurities is not necessary as the levels of elemental impurities from various sources are not expected to exceed the permitted daily exposure 30% threshold levels.

The finished product is released on the market following traditional final product release testing. The procedures for analytical methods used were provided. The non-compendial analytical methods were validated according to current ICH guidance. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data on five commercial scale batches have been provided. All product batches were produced from active substance manufactured with the proposed synthesis method. All batches met the proposed commercial specification. In addition batch data from numerous batches manufactured during development has been presented and all results met the specification at the time of release.

Stability of the product

Stability data from six batches manufactured at the commercial finished product sites packaged in both the proposed closure systems (bottles and blisters) and stored at long term (25 °C / 60 %RH), intermediate (30 °C / 75 %RH) and accelerated (40 °C / 75 %RH) conditions. Three of these batches are the primary stability batches that were made using active substance manufactured at the synthesis development site; the other 3 batches are full commercial scale batches that were made using active substance manufactured at the commercial site by the final commercial synthesis process.
Stability data for the primary stability batches packaged in bottles and blisters up to 24 months at long-term and intermediate conditions and for six months at accelerated conditions are available.
Stability data for the full commercial scale batches, up to 12 months in HDPE bottles and blisters, under long term and intermediate conditions and up to six months under accelerated conditions are available.
It is noted that storage conditions 30 °C / 75 %RH are not according to ICH guideline conditions, however, since the long- term (25 °C / 60 %RH) and accelerate studies (40 °C / 75 %RH) were performed according to ICH conditions and the product does not show any instability, this slight deviation is no cause of concern. The stability studies will be continued post-approval for product batches under long-term storage conditions (25 °C / 60 % RH and 30 °C/75% RH), in accordance to the protocols presented in 3.2.P.8.1.

The stability batches were tested for appearance, assay, chromatographic purity, dissolution, water content, solid state and microbiological purity. The test methods used for stability testing were the same as the proposed methods for release specification, except for one additional test of solid state by XRD. The method description and validation report for the XRD method is provided. The analytical methods were shown to be stability indicating by testing products subjected to forced degradation studies. The results met the specifications and no substantial stability related changes or trends were observed during storage of the product at the different storage conditions.

The same six stability batches were studied under stress conditions at 50 °C through 3 months of storage. A slight increase in one specified degradation product and total degradation products was observed at stress conditions. However, all the specified, unspecified, and total degradation products were within specifications.

Moreover, to challenge the solid state stability of the finished product, an open dish stability study under stressed conditions (high temperature and humidity) was performed. All data available to date confirm that the solid state of the finished product is very stable, when packaged in the proposed container closure system and stored at long-term storage conditions. Although open dish studies have demonstrated that the water content of the finished product has no impact towards the solid state under long term storage conditions, a moisture protective container closure system is part of the control strategy to prevent water uptake by the finished product during storage and additionally ensures that the product will meet the proposed chromatographic

purity, dissolution, and solid-state finished product specifications throughout shelf life. Therefore, the applicant's proposal to maintain the storage condition of "Store in original package in order to protect from moisture" (SmPC 6.4) is acceptable.

In addition, since a hold time for the intermediate has been established, two pilot finished product batches were manufactured at the development sites using aged intermediate batches and have been placed on stability under ICH recommended storage conditions (i.e., end-to-end stability). The intermediate batches, packaged in its commercial container closure system, had been stored for 12 months at 30 °C/75% RH before being processed into finished product. The packaging of the batches were the same as intented for marketing (HDPE bottle and PVC-PCTFE/Alu blister). Stability data from the two pilot finished product batches produced from intermediate previously stored for 12 months (end-to-end stability) met the specifications upon storage under long-term and accelerated conditions. It is therefore justified in line with the requirements defined in the Guideline EMA/CHMP/QWP/24074/2015) to calculate the expiry date of the finished product from the date that the intermediate is mixed with the tablet excipients.

An in-use stability study has been performed that simulates the daily use of the product by the patient. In-use stability data on finished product in HDPE bottles at the initial time of the primary stability batches was presented. After opening and closing during the 30-day in use period, results for all tested parameters: appearance, water content, solid state, solid state by XRD and NIR, assay, chromatographic purity and dissolution meet the proposed commercial shelf-life specification. Furthermore the applicant commits to conduct in-use stability study at the end of shelf life of these batches according to the protocol presented in 3.2.P.8.1. The currently available stability data indicate that the finished product remains stable for 6 weeks at 25 °C /60% RH and 30 °C / 75 % RH during the in-use studies at the initial time point when stored in the proposed commercial packaging. Considering the demonstrated stability profile of the product, it is not considered necessary to specify an in-use shelf-life for the finished product in HDPE bottles in the SmPC.

A photo-stability study has been conducted according to ICH Q1B on the three commercial scale stability batches. The product is not considered as sensitive to light and no special storage condition is warranted with regard to protection from light.

Based on the overall stability data presented the proposed shelf-life of 2 years and the storage condition "Store in original package in order to protect from moisture" (SmPC 6.3 and 6.4) is accepted.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical program was consistent with the proposed indication (non-metastatic castration-resistant prostate cancer), route of administration (oral) and dosing regimen (240 mg/day). The nonclinical development program adhered to the requirements of the ICH S9 guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals. The nonclinical safety package included chronic toxicity and male fertility assessment. For nonclinical safety pharmacology and repeat-dose toxicology evaluations, the rat was chosen as the rodent species and the Beagle dog was chosen as the non-rodent species based, in part, on the similarities in the in vitro and in vivo metabolic profile between these species and human. Species selection for pharmacodynamic and safety evaluations was further supported by pharmacological/toxicological effects on androgen-dependent reproductive organs of adult male animals.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Applicant has conducted primary pharmacodynamic studies to demonstrate binding and inhibitory properties of apalutamide against the AR, selectivity versus other nuclear HRs, mechanism of action in prostate cancer cells, and the pharmacodynamic and antitumor effects of the molecule in animal models.

Apalutamide was shown to bind directly to the AR in competition binding studies in LNCaP/AR(cs) cells with an affinity of 16 nM. However, absolute binding affinities of apalutamide for the androgen receptors of rat, mouse and dog were not determined. The homology of amino acids sequence of ligand binding domain of the protein among species supports binding affinity of apalutamide to AR could be similar across species. The Applicant claims that determination of relative AR binding across species is not expected to have an impact in the interpretation of preclinical or clinical findings, which is endorsed based on studies in vivo.

Apalutamide is shown to be selective for AR versus other nuclear HRs and does not have agonist activity in the absence of androgen.

It has been demonstrated that apalutamide impairs nuclear translocation of the AR in LNCaP/AR(cs) cells, inhibits AR binding to the enhancer regions of AR-dependent genes (PSA and TMPRSS2) and antagonizes androgen-mediated induction or repression of mRNA expression levels of 13 AR-regulated transcripts (TMPRSS2, PSA, CaMK2N1, AMIGO2, PLD1,NOV, BDNF, STEAP4, ORM1, SLUG, HPGD, FKBP and NCAPD3).

Clinically relevant effects mediated by induction or repression of AR-regulated transcripts were characterized in in vivo pharmacology and toxicology studies.

In in vitro studies, apalutamide was found to be more potent than the first-generation AR inhibitor, bicalutamide, and was found not to have agonist activity observed for bicalutamide. Apalutamide was also found to be comparable to enzalutamide (in in vitro studies.

Apalutamide at ≥10 mg/kg showed dose-responsive antitumor activity in castrated mice bearing LNCaP/AR(cs) xenografts tumors. The efficacy of apalutamide was also compared to bicalutamide and enzalutamide. While the effect of bicalutamide in this model was largely restricted to growth inhibition rather than tumor regression, apalutamide and enzalutamide, at the same dose level (10 mg/kg/day), caused tumor regressions greater than 50%. However, at 10 and 30 mg/kg/day, apalutamide demonstrated superior efficacy versus enzalutamide as measured by the fraction of animals exhibiting more than 50% reduction in tumor volume. Greater efficacy was observed for apalutamide despite lower exposures of apalutamide relative to enzalutamide at this dose.

Mutations in the ligand-binding domain of AR have been described in 10% to 20% of patients who have progressed on the first-generation antiandrogen therapies as flutamide and bicalutamide (e.g., L701H, W741C, H874L, T877A) and have also been associated with resistance to next-generation AR-directed therapies such as enzalutamide and apalutamide (AR F877L and AR T878A). Additionally, different studies have shown ARF876L mutation converts AR antagonists to agonists. Clinical relevance of mutation associated to enzalutamide and apalutamide resistance (ARF877L) has been assessed in clinical trials and results suggest that ARF877L mutation is very less prevalent in NM-CRPC setting and expected to have minimal clinical impact to apalutamide treatment.

Four metabolites of apalutamide identified in preclinical species (metabolite M1, JNJ-56142047 [M2], JNJ-56142060 [M3] and JNJ-56142021 [M4]) were assessed for their on-target effects against the AR. Metabolites M1, M2 and M4 were approximately 30-fold less potent against AR than apalutamide. Metabolite M3 was the most potent AR inhibitor, but was still 3-fold less potent than apalutamide.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies were performed to assess the potential of apalutamide to interact with different receptors, channels and transporters. Apalutamide and metabolite JNJ-56142060 (M3) have been shown to be inhibitors of the GABAA-gated chloride channel at clinically relevant concentrations (IC50 of 3.0 and 3.2 µM, respectively). Additionally, in a tissue-based functional assay for the GABAA receptor, an apalutamide IC50 of 0.88 µM was determined. Other minor metabolites including M1, JNJ-56142047 (M2), and JNJ-56142021 (M4) were considered inactive with respect to off-target GABAA effects.

Safety pharmacology programme

Seizures/convulsions have been observed at high apalutamide doses in general toxicology studies in dogs (≥ 25 mg/kg/day) and mice (≥ 175 mg/kg/day) and are considered to be mediated by off-target inhibition of GABAA currents. The NOAEL determined in these studies for convulsions were 10 mg/kg/day in dogs and 100 mg/kg/day in mice, which represent low safety margins (2.2 and 1.3 for apalutamide and the metabolite M3, respectively, based on Cmax values) to discard the risk of seizures in patients. In fact, seizures have been also observed in patients treated with apalutamide and enzalutamide and the effect is described in the SmPC.

Next to seizures, other CNS-related clinical signs were noted after repeated doses in dogs (e.g. tremors, wobbly gait, ataxia) at non-tolerated doses (≥25 mg/kg/day). The NOAEL (10 mg/kg/day) for CNS effects determined in

the 13-and 39-week repeat-dose toxicology studies in dogs provides a safety margin of 4.3 for apalutamide and 1.5 for the metabolite M3, or 6.5 and 2.4 considering the difference in protein binding between species and based on AUC values. No test article-related CNS effects were observed in a full functional observation battery (FOB) assessment or in the 26-week toxicity study in male and female rats at doses (up to 150 mg/kg) exceeding the apalutamide clinical exposure level approximately 5-fold (or 8.5 -fold considering the difference in protein binding between species). The systemic levels of JNJ-56142060 (M3) were not determined in the FOB study, but toxicokinetic data from the 26 week toxicity studies indicate that exposure level to M3 in rats receiving 150 mg/kg of apalutamide is much lower than level reached in human treated with 240 mg/day (0.2 fold). Thus, the M3 exposure in animals (rats and dogs) at the NOAEL for CNS effects compared to the clinical exposure is considered to be low to disregard the risk of developing CNS effects in patients. However, as the incidence of tremor, gait disturbance, and ataxia was low and similar between the treatment arms (placebo and apalutamide) in the Phase 3 clinical Study ARN-509-003, additional non-clinical studies are not required.

On the other hand, cognitive and memory impairment have been associated to hormonal deprivation, but no evidence of impairment has been found in nonclinical and clinical trials with apalutamide.

Noteworthy, the inhibition of the 5-HT2B receptor-ligand interactions was 25% at a concentration of 10 µM. Activation of 5-HT2B receptor agonists has been associated with the valvular heart disease (Rothman RB et al., Circulation, 2000). Rothman RB et al. has concluded that medications with serotonergic activity and their active metabolites should be screened for agonist activity at 5-HT2B receptors and that clinicians should consider suspending their use of medications with significant activity at 5-HT2B receptors (Rothman RB et al., Circulation. 2000, Rothman RB and Baumann MH, Expert Opin Drug Saf. 2009). The risk for valvular heart disease risk due to 5-HT2B binding activity of apalutamide and its metabolite is considered low based on the binding affinity of apalutamide to 5-HT2B receptor is considered low and the concentration 10 µM was 19-fold higher than the free steady-state efficacious plasma exposure in man at a dose of 240 mg per day, pivotal toxicology studies in rats and dogs revealed no signs of apalutamide or its major metabolite M3 treatment related cardiac pathologies and the histopathologic examinations of the heart valves revealed no valvulopathies and the incidence of valvular heart disease observed in clinical Study ARN-509-003 was lower in the apalutamide arm than in placebo.

Apalutamide and M3 inhibited the hERG current at concentration that exceeded clinical exposure by 7 fold. But they did not prolong action potential in canine Purkinje fiber assay at concentrations around 50 times the anticipated unbound Cmax plasma exposure of apalutamide and metabolite M3 in men with CRPC treated with apalutamide at 240 mg/day. Apalutamide at 3 and 10 µM, but not at 30 µM, induced a statistically significant ($P<0.05$) reduction in APA at a 2s BCL (Mean; 0.5 and -1.7 mV, respectively) and the shape (slope) of the apalutamide curve differs quite remarkably from those of vehicle control and metabolite JNJ-56142060 (M3). These changes are not supported by the other parameters that characterize the action potential as inhibition of the Na+ or the Ca2+ channels and changes in the heart rate and PQ interval in telemetry study in dogs, and therefore are considered biologically insignificant. The changes of the slope of the apalutamide curve are clarified by the biological variability of the cell content within Purkinje fibre.

Apalutamide was also evaluated for possible cardiovascular effects following single oral administration in conscious telemetered dogs. Following administration of apalutamide at 10, 20 and 40 mg/kg, correlation between apalutamide and prolonged QT interval were observed 2 hours post dose. This finding is considered coincidental due to the inter-individual variation within the group and individual pre-dose variations and thus, no clinically relevant.

A dedicated respiratory safety pharmacology study in rats did not reveal any concerns following a single-dose administration of apalutamide.

Pharmacodynamic drug interactions

Non-clinical pharmacodynamic interaction studies were not conducted with apalutamide.

2.3.3. Pharmacokinetics

Nonclinical studies of the pharmacokinetics of apalutamide and its M3 and M4 metabolites were conducted after both single- and repeat-dosing in CD-1 mice, Sprague-Dawley rats and Beagle dogs.

The oral formulation used in most of the PK/TK evaluations of apalutamide was a nonaqueous lipid-based solution of apalutamide. It is the same formulation as the apalutamide drug product used in the in vivo pharmacodynamic studies and in the early clinical studies (ie, softgel capsules, 30 mg). The Marketing Authorisation Application (MAA) is for 60mg immediate –release oral film-coated tablet. Pharmacokinetic profiles of both formulations have not been directly compared in non-clinical species, but in the dog formulation study, a formulation prototype of the currently marketed tablet had an relative bioavailability (Frel) of 117% compared to the soft gel capsule. Since most toxicities found in animals were observed at doses that provide low safety margins to disregard the effects in patients, minimal increment in bioavailability of the drug with the new formulation does not alter the relevance of the safety data provided. Moreover, the tablet and capsule formulations were demonstrated to be bioequivalent in a human relative bioavailability study.

In mice, rats, and dogs, apalutamide is a low clearance molecule (0.5 to 1.3 mL/min/kg) with a moderate volume of distribution (2.1 to 2.8 L/kg). Oral bioavailability of the lipid-based emulsion was high in the mouse (93% at 3 mg/kg) and approximately 100% in the dog (at 10 mg/kg). It was not assessed in the rat.

Following single dose, apalutamide, M3 and M4 displayed dose-proportional pharmacokinetics over a wide range of doses in mice and rats including and above the therapeutic range. In dogs, systemic exposure for apalutamide increased slightly more than dose-proportional over the entire dose range (5-40 mg/kg), systemic exposure of M3 was slightly less than dose-proportional between 2.5 and 10 mg/kg and slightly more than dose-proportional between 10 and 20 mg/kg and systemic exposure of M4 was more than dose-proportional between 2.5 and 5 mg/kg and dose-proportional between 5 and 10 mg/kg. At lower doses of repeat administration in rats, exposure to apalutamide was generally dose-proportional, but at higher doses exposure to apalutamide did not increase or was less than dose-proportional, whereas metabolite exposure continued to rise and was often greater than dose-proportional. Clinical exposure of apalutamide and N-desmethyl apalutamide were approximately dose proportional over the apalutamide dose range of 30 to 480 mg per day (0.125 to 2 times the recommended dosage).

Exposure (both Cmax and AUC) was lower after repeat administration than after single dosing in mice but accumulation of apalutamide, M3 and M4 was evident in rats and dogs after repeat doses. In dogs, concentrations were similar on Days 28, 91, 182, and 273 indicating that steady-state had been achieved by Day 28.

M3 and M4 peak plasma concentration were delayed in mice (24-48 hours) and dogs (21-72 hours) compared to apalutamide peak plasma concentrations (2-8 hours). However, maximum plasma concentrations of apalutamide, M3 and M4 were achieved between 8 and 12 hours postdose in rats.

Metabolites to parent ratios increased with dose in rats, they were not dose dependent after single administration in dogs and they decreased with increasing doses after longer exposure in dogs.

The pharmacokinetics appear to be comparable between male and female mice and dogs. However, exposure of apalutamide was higher in females than in male rats and differences in exposure increased after repeat dose,

whereas M3 levels were higher in males than in female rats. The effect of sex on exposure is not relevant because apalutamide is only indicated in men.

Apalutamide was widely distributed throughout with maximal concentrations in most tissues 4 to 12 hours postdose. Radioactivity was greatest in abdominal and brown fat, liver, kidney cortex and medulla, adrenal cortex, pancreas, and Harderian gland and lowest in the lens of the eye, brain and bone surface. A small amount of residual radioactivity was retained in the skin 504 hours postdose. Binding of drug-related material to melanin is unlikely because radioactivity levels in pigmented tissues were comparable to the nonpigmented skin and there was no retention of radioactivity in the uveal tract. Concentrations of apalutamide, M3 and M4 were approximately dose proportional in brain. Concentrations of apalutamide and M3 in plasma were dose proportional in mice and greater than dose-proportional in dogs. Apalutamide and M3 brain-to-plasma ratios were lower in mice (31.5-43.9% for apalutamide and 47.0-50.6% for M3 at 24 hours postdose) and rats (76 % for apalutamide and 53% for M3) than in dogs (~1 for apalutamide and 1.1-1.4 for M3).

The free fractions of apalutamide and M3 in plasma samples were, respectively, 8.2% and 9.4% in mouse, 7.2% and 8.6% in rat, 6.3% and 8.2% in dog, 11.4% and 13.2% in rabbit, and 4.2% and 5.1% in human at concentration over a test range of 0.1 to 30 µg/mL.

The blood distribution of apalutamide was similar as M3 for all species, with the majority of the compounds bound to plasma proteins (0.50 to 0.685), but also a considerable fraction distributed to blood cells (0.285 to 0.424).

Apalutamide is extensively metabolized in rats, dogs and humans. Apalutamide represented only 1% to 3% of the dose in urine, and 2% to 8% in feces. The metabolic pathways for apalutamide are comparable between rat, dog, and human.

Metabolites were formed directly from apalutamide by several reaction types: oxidation, oxidative desulfuration, nitrile hydrolysis, cysteine-glycine condensation, cysteine condensation, amide hydrolysis, and ring-opening/hydrolysis.

In human, JNJ-56142060 (M3) and JNJ-56142021 (M4) are considered major (41%) and minor (2.7%) human plasma metabolites. JNJ-56142060 (M3) (41%) is also found in rats (<10%) and dogs (51%), supporting the relevance of these species for the preclinical safety program of apalutamide. Adequate coverage of human exposure for M3 was established in the dog but not in the rat toxicology studies.

In rat and human, M3 is derived directly from parent drug (N-demethylation), however in dog, M6 (N-(hydroxymethyl)benzamide), an oxidation product of parent drug, was the precursor to M3.

The formation of M3 (amide) is mediated predominantly by CYP2C8 and to a lesser extent by CYP3A4, and the conversion of M3 to M4 (carboxylic acid) is most likely catalyzed by carboxylesterases.

In humans the urinary pathway is the major route of excretion of apalutamide (64.2%). However, apalutamide is mainly eliminated in faeces in rats (58.2%) and excretion of apalutamide in dogs is divided equally between urine and feces.

M4 accounted for the majority of excreted radioactivity in urine (rat, dog, and human), faeces (rat and dog), and rat bile, thus N-demethylation of the N-methylbenzamide moiety to an amide (M3), followed by amide hydrolysis to a carboxylic acid (M4) and direct amide hydrolysis of the N-methylbenzamide moiety to M4 are the principal metabolic clearance pathways of parent drug. The formation of M20 (amide) by N-demethylation of M19 (ring opening/hydrolysis product of apalutamide) is an important metabolic clearance pathway in dogs and humans. M20 is more abundant in urine than all other excreted metabolites (except M4).

The similarities in the in vitro and in vivo metabolic profile between rats, dogs and men support the adequacy of these species for toxicological assessment of apalutamide.

In vitro studies showed that apalutamide and M3 are moderate to strong CYP3A4 and CYP2B6 inducers (SmPC section 4.5).

Apalutamide and M3 are moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. In humans, apalutamide is a strong inducer of CYP3A4 and CYP2C19, a weak inducer of CYP2C9 and it did not cause clinically meaningful changes in exposure to the CYP2C8 substrate.

Apalutamide and M3 were substrates for P-gp/multidrug resistant 1 (MDR1), but not for BCRP, OATP1B1, and OATP1B3. Both compounds are inhibitors of P-gp/MDR1 and BCRP, OCT2, OAT3 and MATE-1 at clinically relevant concentrations. Interactions with other transporters (OATP1B1, OATP1B3 and MATE-2K) are not clinically relevant. Apalutamide and M3 did not inhibit OAT1.

2.3.4. Toxicology

Single dose toxicity

The MTD of apalutamide following a single oral dose administration in male animals exceeded the highest single dose tested, i.e. > 2,000 mg/kg in male rats and > 40 mg/kg in male dogs. The MTD of apalutamide following single oral dose administration was 100 mg/kg in male and female mice.

Repeat dose toxicity

The toxicity of apalutamide after repeated oral administration was studied in pivotal toxicology studies with dosing up to 26 weeks in male rats and 39 weeks in male dogs.

Table 1. Repeat-dose studies in rats:

Study ID	**Species/ Sex/**	**Number /Group**	**Dose**	**Route**	**NOEL/ NOAEL (mg/kg/ day)**	**Major findings**
14-day toxicity Aragon, VUM00002, non-GLP	S-D Rat (M)	**5**	0 (vehicle), 0 (water), 150, 300, or 600 mg/kg/day	orally (by gavage)	150	Mortality at 300 and 600 mg/kg/day, Clinical signs: salivation, piloerection, thin appearance, hunched posture, aggressiveness, abnormal breathing, fecal/urine staining, and vocalization. At ≥ 150 mg/kg/day decrease in body weight. hematology parameters: decreases in erythrocytes, hemoglobin, and hematocrit,

						increases in reticulocytes and platelets; and increases in white blood cells. Decrease in size and weight of prostate gland, seminal vesicles and epididymides.
A 28-Day Oral Toxicity Study with a 14-Day Recovery Period (Aragon, VUM00004, GLP)	S-D Rat (M)	10	0 (water), 0 (vehicle), 50, 150, or 250 mg/kg/day	orally (by gavage)	50	The majority of the 250 mg/kg/day animals were found dead on Day 3. At ≥ 50 mg/kg/day: Decreased size and weight of the accessory sex organs, including the epididymides, prostate gland, and seminal vesicles. Hematology parameters: At 150 mg/kg/day decreases in erythrocytes, hemoglobin, and hematocrit, increases in reticulocytes and platelets; and increases in white blood cells. Chemistry parameters: increased cholesterol (up to 3-fold), GGT, protein, albumin, globulin, urea nitrogen, creatinine, calcium, and phosphate. Hyperplasia of the interstitial (Leydig) cells.
A 13-Week Oral Toxicity Study with a 30-Day Recovery Period (Aragon, TX-509-1001, GLP	S-D Rat (M)	15	(vehicle), 25, 50, or 100 mg/kg/day	orally (by gavage)	100	5 preterminal incidental deaths, Hematology parameters: decreases in red cell mass (up to 15%), increase in reticulocytes and red blood cell distribution, platelets, fibrinogen, white blood cells, and lymphocytes, clinical chemistry: dose-related increases in cholesterol (up to 2.8-fold), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total protein, albumin, and globulin,

						creatinine, and ALP (< 2-fold). Decrease in the size of the prostate gland and seminal vesicles, Hyperplasia of the interstitial (Leydig) cells.
A 26-Week Oral Toxicity Study (Janssen, TOX10838, GLP)	S-D Rat (M)	20	0 (vehicle), 25, 75, or 150 mg/kg/day	orally (by gavage)	25	Less gain of body weight at 75 and 150 mg/kg/day (15.1%, and 15.0%), Hematology parameters: decreases in red cell mass (up to 20%) with increases in reticulocytes, platelets, fibrinogen, white blood cells, and lymphocytes. clinical chemistry: increases in cholesterol (up to 3.3-fold), creatinine, blood urea nitrogen, and ALP (< 2-fold). At necropsy, a dose-related decrease in the size and/or weight of the epididymis, prostate gland, and seminal vesicles was observed. hyperplasia of testicular interstitial (Leydig) cells which progressed to benign interstitial (Leydig) cell adenomas. At 150 mg/kg/day, thymus weights were increased.
A 26-Week Oral Toxicity Study with a 2-Month Recovery Period (Janssen,	S-D Rat (F)	20	0 (vehicle), 25, 50, 100, or 150 mg/kg/day	orally (by gavage)	< 25	10 study animals died (1 control, 3 at 25 mg/kg/day, 1 at 50 mg/kg/day, 1 at 100 mg/kg/day, and 4 at 150 mg/kg/day). Hematology parameters: At ≥ 25 mg/kg/day, decreases in red cell mass (up to 20%) and increases in white blood cells and lymphocytes. At ≥ 100 mg/kg/day, additional hematology changes consisted

TOX10897, GLP)						of increases in MCV, MCH, RDW, and increases in monocytes. Fibrinogen was increased Clinical chemistry: dose-related increases in cholesterol (up to 2.85-fold), total protein, albumin, and globulin. macroscopic pathology findings were observed in the ovaries(masses and pale foci at ≥ 100 mg/kg/day), mammary gland (thickness or nodule formation), adrenal gland, and pituitary gland (both enlarged). histopathology, ovarian tumors (granulosa cell and/or theca cell origin) were present at all doses: 1 malignant granulosa cell tumor at 25 mg/kg/day, 1 benign thecoma at 50 mg/kg/day, 11 thecomas (benign or malignant) and/or benign granulosa cell tumor at 100 mg/kg/day, and 9 thecomas (benign or malignant) at 150 mg/kg/day. In addition, interstitial cell hyperplasia and absence of corpora lutea were noted in many of these ovaries. Other non-neoplastic findings at all doses included hypertrophy of the uterine wall; dilatation (and galactocele), hypertrophy, and vacuolation affecting the mammary gland; hypertrophy of the cortex in the adrenal gland; hyperplasia in the pituitary gland; and hepatocellular hypertrophy in the liver. Additionally, increased

						hematopoiesis.

Table 2. Repeat-dose toxicity studies in dogs:

Study ID	**Species /Sex**	**Number /Group**	**Dose**	**Route**	**NOEL/ NOAEL (mg/kg/day)**	**Major findings**
A 28-Day Oral Toxicity Study with a 28-Day Recovery Period (Aragon, VUM00005, GLP)	male dogs	5	0 (vehicle), 5, 10, or 25 mg/kg/day	orally (by capsule)	10	Three animals in the 25 mg/kg/day group were euthanized by Day 9 due to seizures. Clinical signs: intermittent tremors and decreased activity. Convulsions were observed at 25 mg/kg/day. Increase in cholesterol was present at 5 and 10 mg/kg/day. Necropsy findings: decreases in size or weights of the prostate gland, epididymides, and/or testes. Hypo/aspermatogenesis in the testes at 10 mg/kg/day.
A 13-Week Oral Toxicity Study with a 60-Day Recovery Period (Aragon, TX-509-1002, GLP)	male dogs	5	2.5, 5, or 10 mg/kg/day	orally (by capsule)	5	No mortality occurred and no test article-related clinical signs. 31% less body weight at 10 mg/kg/day. At ≥ 2.5 mg/kg/day, increases in cholesterol (up to 1.4-fold) and HDL. Decreases in organ weights were noted for the prostate gland and epididymides at dose levels ≥ 2.5 mg/kg/day and in the testes at 10mg/kg/day. Microscipic findings in prostate (atrophy), epididymides (atrophy and hypospermia) and testes (degeneration of seminiferous tubules and hypospermia) at ≥ 2.5

						mg/kg/day.
A 39-Week Oral Toxicity Study (Janssen, TOX10839, GLP)	male dogs	4	2.5, 5, or 10 mg/kg/day	orally (by capsule)	< 2.5	No mortality occurred and there were no test article-related clinical signs. Mean body weight also was decreased (0.92x, 0.88x, and 0.88x at 2.5, 5, and 10 mg/kg/day). Clinical chemistry : increases in cholesterol (up to 1.7-fold) at ≥ 2.5 mg/kg/day and ALP (up to 3.5-fold) at ≥ 5 mg/kg/day. Decreases in weights for the prostate gland, epididymides, and kidneys at ≥ 2.5 mg/kg/day. Microscipic findings in prostate (atrophy), epididymides (atrophy) and testes (degeneration/atrophy of seminiferous tubules and reduced spermatogenesis and interstitial (Leydig) cell hypertrophy) at ≥ 2.5 mg/kg/day. Bile duct/oval cell hyperplasia observed at all dose levels.
A 13-Week Oral Toxicity Study with a 1-Month Recovery Period (Janssen, TOX10895, GLP)	Female dogs	4	2.5, 5, or 10 mg/kg/day	orally (by capsule)	10	No mortality occurred and no clinical signs or effects on body weight, food consumption, ECG, hematology, coagulation, or urinalysis parameters. Clinical chemistry: increases in cholesterol (up to 1.2-fold) at ≥ 2.5 mg/kg/day and in ALP at 10 mg/kg/day (up to 2.5-fold). Decreases in ovary and uterus weights.

The selection of species and duration of the studies are appropriate for the proposed indication. Recovery periods were included in the 13-weeks male rat study (30 days), 13-weeks male dog study (2 months) and 26 weeks female rats study (2 months) and are recommended, but missing, in pivotal toxicity studies, namely the 26 weeks in male rats and 39 weeks in dogs. The adequacy of including recovery periods in pivotal toxicity studies is supported by the detection of effects such as bile duct/oval cell hyperplasia in dogs in the longer studies and because non-metastatic castration-resistant prostate cancer may include earlier stage prostate cancer and patient populations outside the scope of the ICH S9. However, considering apalutamide-related findings were reported to partially or fully recover in 13-weeks male rat and dog studies and the 3Rs (Replacement, Reduction and Refinement) principle, additional studies to assess the reversibility of finding in longer toxicity studies are not required. In addition, the Applicant should perform long term carcinogenicity studies, which may be useful to assess the clinical relevance of hyperplasias observed in dogs (see RMP).

In repeat-dose studies, test article-related mortality was observed after repeated dosing at ≥ 250 mg/kg/day in rats, at ≥ 25 mg/kg/day in male dogs and at 20 mg/kg/day in female dogs. At MTD levels after repeated dosing in rats and dogs, at which no test article-related mortality was observed, animal-to-human exposure ratios based on AUC were 5.7 and 3.0, respectively.

Lower body weight gain and food consumption were reported for male rats and dogs at most dose levels and for female dogs above the MTD. A higher body weight gain was observed in female rats. Weight decrease and decreased apatite were also observed in humans after treatment with apalutamide.

Apalutamide affected the male reproductive system (atrophy of secondary sex glands; degeneration of seminiferous tubules and hyperplasia/hypertrophy of interstitial (Leydig) cells), mammary glands (alteration of the male mammary gland to a female tubuloalveolar morphology), pituitary gland (increases in the weights and hypertrophy in the pars distalis), adrenal glands (increments in the weights and cortical hypertrophy), and thymus (increases in the weights), at ≥ 25 mg/kg/day in rats and/or at ≥ 2.5 mg/kg/day in dogs. Plasma exposure levels of apalutamide at these doses were slightly below (male dog) or around (male rat) the apalutamide exposure in individuals with CRPC. These changes were partially to fully reversible. In the 26-week repeat-dose toxicology study in male rats, changes in the rat testis progressed to benign interstitial (Leydig) cell adenomas.

Serum cholesterol was dose-relatedly increased in rat studies (up to 3-fold) and to a lesser extent in dogs (up to 1.7-fold). Increases in cholesterol have been reported for other anti-androgenic drugs as enzalutamide.

Increased white blood cells, especially lymphocytes and a decrease in red cell mass were consistently observed in rat studies. Fibrinogen was increased in rats in longer studies (≥3 months) at ≥25 mg/kg. Increases in serum total protein, albumin, globulin, urea nitrogen, creatinine, triglycerides, HDL, LDL and glucose were observed in rat studies at ≥25 mg/kg. Other changes in hematology (e.g. increase or decrease in APTT and PT in male or female rats, respectively) and serum parameters (e.g. increases in GGT, calcium, phosphate and ALT) were not observed consistently throughout the studies and mostly observed at high doses (150 mg/kg) in shorter-term repeat-dose studies (≤28 days).

Another target organ of toxicity after prolonged treatment with apalutamide is the liver, as evidenced by dose-dependent increased liver weights and/or reversible hepatocellular hypertrophy in rats and bile duct/oval cell hyperplasia in the male dog observed after 39 weeks of dosing. Recovery of the bile duct/oval cell hyperplasia in the male dog was not assessed. Increases inALP in rats and dogs were shown to be fully reversible. Increases in ALP and ALT have also been associated with other anti-androgenic drugs.

Rat thyroid alterations (organ weight increase, follicular hypertrophy or follicular hyperplasia or both) were observed in the 28-day study in males and the 26-week study in females.

Other findings observed in some of the repeat-dose studies in rat and dog (decreases in salivary gland weights in 28-day male rat study; increased heart and kidney weights in 26-week female rat study; and decreased kidney weights in 39-week male dog study) were often not confirmed in longer-term toxicology studies at similar doses levels and/or not accompanied by histopathological changes.

The toxicity profile of apalutamide was generally consistent across studies with more target organs in rats relative to dogs.

Genotoxicity

Apalutamide and its major metabolite JNJ-56142060 (M3) were tested in three standard assays for genotoxicity: an in vitro Ames test, an in vitro chromosome aberration test in human peripheral blood lymphocytes, and an in vivo micronucleus assay in rats. The results of all these studies were negative.

Apalutamide and metabolite JNJ-56142060 (M3) did not induce mutations in the bacterial reverse mutation (Ames) assay and were not genotoxic in either the in vitro chromosome aberration test or the in vivo rat micronucleus assay. Apalutamide was not genotoxic in the in vivo rat Comet assay. The inactive metabolite JNJ-56142021 (M4) did not induce mutations in the Ames assay and was weakly positive in the in vitro chromosome aberration test. Since apalutamide tested negative in two in vivo studies (rat micronucleus assay and rat Comet assay) with adequate exposure to JNJ-56142021 (M4) in plasma and liver, JNJ-56142021 (M4) is considered non-genotoxic in vivo.

Carcinogenicity

According to the ICH S9 guideline, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer. It is noted that in the SAWP/CHMP scientific advice (EMEA/H/SA/2344/1/2012/SME/III) carcinogenicity studies as well as repeat-dose toxicity studies longer than 3 months were not required, but pending the results of the Phase III studies. The company has conducted 6 and 9 month toxicity studies in rats and dogs, respectively, but no carcinogenicity studies. Clinical studies seem to indicate that the product might provide a clinical benefit on NM-CRPC patients with high risk of developing metastasis and the ICH S1A states that in cases where the therapeutic agent is successful and life is significantly prolonged, there may be later concerns regarding secondary cancers. In addition, considering the observed hypertrophic effects caused by apalutamide in the repeat-dose toxicity studies, even though the compound is not genotoxic, carcinogenic studies should be conducted. The Applicant has planned a nonclinical carcinogenicity program with apalutamide. The final report of a 2-year carcinogenicity study in the rat will be available by the third quarter of 2021 and the final report of a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse will be available by the third quarter of 2020 (see RMP).

Reproduction Toxicity

Considering the indication and patient population, prostate cancer in males, a full reproduction toxicity programme is not warranted. Only a male fertility study in rats was performed. This showed a decrease in epididymal sperm concentration and motility and in copulation rates along with reduced weights of the secondary sex glands and epididymis at ≥ 25 mg/kg/day (0.85 fold the human exposure based on AUC), and a lower fertility rate and a reduced potential for generating viable offspring at 150 mg/kg/day (5.7 times the human exposure based on AUC). Therefore, based on animal studies, effects on male fertility cannot be discarded. Effects on fertility in male rats were reversible after 8 weeks from the last apalutamide administration.

Toxicokinetic data

Animal-to-human exposure ratios (Cmax and AUC) for apalutamide and metabolite JNJ-56142060 (M3) were calculated based on animal exposures at the NOAEL and MTD in the 26-week male rat and 39-week male dog toxicology study relative to human reference exposures from a Phase 1b QT/QTc study.

Table 3. Apalutamide and JNJ-56142060 (M3) exposure in male animals (26-week rat and 39-week dog) at the NOAEL and MTD relevant to humans

Species	Dose (mg/kg)	C_{max} (µg/mL)	AUC (µg.h/mL)	Animal-to-Human Exposure Ratio	
				C_{max}	AUC
Apalutamide					
Rat NOAEL (26-week)[a]	25	7.20	135	1.2	1.4
Rat MTD (26-week)[a]	150	27.7	508	4.7	5.1
Dog NOAEL (39-week)[b]	< 2.5	< 3.82	< 86.6	< 0.6	< 0.9
Dog MTD (39-week)[b]	10	18.7	427	3.1	4.3
Human[c]	240 mg	5.95	100	-	-
JNJ-56142060 (M3)					
Rat NOAEL (26-week)[a]	25	0.228	4.58	< 0.1	< 0.1
Rat MTD (26-week)[a]	150	1.4	27.7	0.2	0.2
Dog NOAEL (39-week)[b]	< 2.5	2.99	69.7	0.5	0.6
Dog MTD (39-week)[b]	10	8.32	189	1.4	1.5
Human[c]	240 mg	5.85	124	-	-

Local Tolerance

No local tolerance studies were submitted.

Other toxicity studies

Apalutamide and M3 did not demonstrate phototoxicity in the in vitro Neutral Red uptake assay.

According to the drug product and drug substance specifications, impurities JNJ-56142047 and JNJ-64464920 should be qualified. JNJ-56142047 is considered toxicologically qualified because it is the M2 metabolite of apalutamide and JNJ-64464920 is toxicologically qualified on a repeat-dose toxicology study in rats at a concentration ~4 fold the highest concentration administered to human. The genotoxic potential of JNJ-64464920 was assessed by two (Q)SAR methodologies, DEREK and Leadscope, and no structure alerts were detected. Thus, JNJ-64464920 is considered no genotoxic and no further testing is required.

2.3.5. Ecotoxicity / environmental risk assessment

A complete environmental risk assessment has been performed for apalutamide and no adverse environmental effects are anticipated as a consequence of the use of apalutamide for the treatment of prostate cancer as indicated in the SmPC.

It is noted the PECsw refinement of the applicant is considered not acceptable. The active ingredient is excreted by approximately 88% (De Vries, 2015) and cannot be distributed evenly over 70 days. A PECsw refinement in

phase II tier B is possible taking into account the distribution in the sewage treatment plant with the simple treat model and the complete excretion of the active ingredient. This would result in a PECsw refined of 0.985 µg/L, in contrast to 0.014 µg/L by the applicant. The PECsw refined value based on simple treat model does not alter the conclusions of apalutamide ERA.

A precautionary statement of the potential environmental risks and clear instructions aimed at minimising the quantity discharged into the environment and appropriate mitigation measures is included in the SmPC and PIL.

The following table summarizes the ecotoxicity studies performed with apalutamide.

Table 4.Table: Summary of main study results

Substance (INN/Invented Name): apalutamide/Erleada			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	EMA/CHMP/SWP /44609/2010 Rev.1*.	2.89 at pH 4 2.91at pH 7 2.94 at pH 9	Potential PBT (N) PBT assessment is not necessary (Q6 in EMA QA Guideline).
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.20	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(Y) Apalutamide is considered a potential endocrine disruptor
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	KOC = 673 L/kg (soil) KOC = 744 L/kg (soil) KOC = 760 L/kg (soil) KOC = 889 L/kg (soil) KOC = 516 L/kg (sludge) KOC = 601 L/kg (sludge)	KOC < 10 000 L/kg therefore a Phase II Tier B terrestrial compartment studies are not necessary. Kd, Koc andKdes values for [14C] ARN-509 were determined The Kd values were 42.8, 5.48, 17.6, 4.50, 166 and 215 mL/g for DU soil, RMN soil, MSL soil, PD soil, Wareham activated sludge and New Bedford activated sludge Kdes values for DU soil, RMN soil, MSL soil, PD soil, Wareham activated sludge and New Bedford activated sludge were 55.7, 6.34, 21.6, 5.24, 121 and 170, mL/g
Ready Biodegradability Test	OECD 301	0.59% CO2 evolution was achieved by day 28.	ARN-509 cannot be classified as “readily biodegradable” by the criteria set forth in OECD Guideline 301B
Aerobic and Anaerobic Transformation in Aquatic	OECD 308	$DT_{50,\ whole\ system}$ = 103 days	ARN-509 fulfill the criteria for classification as very persistent

Sediment systems		% shifting to sediment =10% Taunton River (20oC): DT50 (water) = 30 d DT50 (sediment) = >1000 d DT50 (system) = 315 d (SFO) Weweantic River (20oC): DT50 (water) = 32 d SFO) DT50 (sediment) =105 d DT50 (system) = 92 d (SFO)			(vP) in the aquatic environment.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	72h- NOEC	2.4	mg/L	Growth rate (Pseudokirchneriella subcapitata)
Daphnia sp. Reproduction Test	OECD 211	21d-NOEC	1.9	mg/L	Juvenile production (Daphnia magna)
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	3.7	mg/L	Oncorhynchus mykiss
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	>1000	mg/L	

2.3.6. Discussion on non-clinical aspects

Apalutamide is an orally administered AR inhibitor that is a potent and selective antagonist of the AR without significant agonist properties. Apalutamide antagonizes AR signalling through inhibition of AR nuclear translocation and DNA binding to androgen response elements. Gene transcription of the androgen-responsive genes, PSA and TMPRSS2, is inhibited by apalutamide, resulting 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 castrated mice bearing LNCaP/AR(cs) xenografts tumors.

Information on the affinity of apalutamide to AR in the species employed for the assessment of the product would be welcomed post-authorization.

The prominent human plasma metabolite JNJ-56142060 (M3) was also shown to bind directly to the AR, but was 3-fold less potent than apalutamide. Other minor metabolites including M1, JNJ- 56142047 (M2), and JNJ-56142021 (M4) were considered inactive with respect to on-target AR effects.

Secondary pharmacodynamic studies were performed in vitro to assess the potential of apalutamide to inhibit receptors and transporters. Apalutamide and metabolite JNJ-56142060 (M3) have been shown to be inhibitors of the GABAA-gated chloride channel at clinically relevant concentrations. This interaction may be the mechanism for the convulsions observed in general toxicology studies in dogs and mice. Seizures have been also observed in patients treated with apalutamide and enzalutamide and the effect is described in the SmPC.

Next to seizures, other CNS-related clinical signs were noted after repeated doses in dogs (e.g. tremors, wobbly gait, ataxia) at non-tolerated doses. However, no test article-related CNS effects were observed in a FOB assessment or in the 26-week toxicity study in females rats. The M3 exposure in animals (rats and dogs) at the NOAEL for CNS effects compared to the clinical exposure is considered low to discard the risk of developing CNS effects in patients. In the Phase 3 clinical Study ARN-509-003, the incidence of tremor, gait disturbance, and ataxia was low and similar between the treatment arms.

Noteworthy, the inhibition of the 5-HT2B receptor-ligand interactions was 25% and activation of 5-HT2B receptor agonists has been associated with the valvular heart disease. Based on the totality of nonclinical in vitro and in vivo data and supported by clinical observations, the risk for valvular heart disease risk due to 5-HT2B binding activity of apalutamide and its metabolite is considered low.

For cardiac safety pharmacology, apalutamide and M3 inhibited the hERG current at concentration higher than the anticipated highest free concentration in humans and they did not prolong action potential repolarization in isolated canine Purkinje fibbers at concentrations around 50 times higher than the anticipated unbound Cmax plasma exposure of apalutamide and metabolite M3 in men with CRPC treated with apalutamide at 240 mg/day. Apalutamide at 3 and 10 µM, but not at 30 µM, induced a statistically significant reduction in APA at a 2s BCL (Mean; 0.5 and -1.7 mV, respectively) and the shape (slope) of the apalutamide curve differs quite remarkably from those of vehicle control and metabolite JNJ-56142060 (M3). These changes are not supported by the other parameters that characterize the action potential and therefore are considered biologically insignificant. The changes of the slope of the apalutamide curve are clarified by the biological variability of the cell content within Purkinje fibre.

Single oral administration of apalutamide in conscious telemetered dogs was correlated to prolonged QT interval. This finding is considered coincidental due to the inter-individual variation within the group and individual pre-dose variations and thus, no clinically relevant.

In safety pharmacology studies apalutamide had no relevant effects on respiratory systems at clinically relevant exposures at 240 mg.

No pharmacodynamic drug interaction studies have been performed.

The oral formulation used in most of the PK/TK evaluations of apalutamide is a lipid emulsion which is the same formulation as the apalutamide drug product used in the in vivo pharmacodynamic studies and in the early clinical studies. However, a more stable formulation of higher dosage strength and comparable bioavailability was developed. Pharmacokinetic profiles of both formulation have not been directly compared in non-clinical species, but in the dog formulation study, a formulation prototype of the currently marketed tablet had an relative bioavailability (Frel) of 117% compared to the soft gel capsule. Since most toxicities found in animals were observed at doses that provide low safety margins to disregard the effects in patients, minimal increment in bioavailability of the drug with the new formulation does not alter the relevance of the safety data provided. Moreover, the tablet and capsule formulations were demonstrated to be bioequivalent in a human relative bioavailability study.

Pharmacokinetic data support the adequacy of rats and dogs for toxicological assessment of apalutamide, despite adequate coverage of human exposure for M3 was established in the dog but not in the rat toxicology studies.

Regarding mechanisms for drug-drug pharmacokinetic interactions, apalutamide is a substrate of cytochrome P450 (CYP)3A4 and CYP2C8 and metabolite N-desmethyl apalutamide is formed by these enzymes. Apalutamide and its N-desmethyl metabolite are moderate to strong CYP3A4 and CYP2B6 inducers, are moderate inhibitors

of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. In humans, Apalutamide is a strong inducer of CYP3A4 and CYP2C19, a weak inducer of CYP2C9 and it did not cause clinically meaningful changes in exposure to the CYP2C8 substrate. Apalutamide and its main metabolite M3 do not affect CYP1A2 and CYP2D6 at therapeutically relevant concentrations.

Apalutamide and M3 were substrates for P-gp/multidrug resistant 1 (MDR1), but not for BCRP, OATP1B1, and OATP1B3. Both compounds are inhibitors of P-gp/MDR1 and BCRP, OCT2, OAT3 and MATE-1 at clinically relevant concentrations. Interactions with other transporters (OATP1B1, OATP1B3 and MATE-2K) are not clinically relevant. Apalutamide and M3 did not inhibit OAT1.

The general toxicology studies were conducted in rats up to 26 weeks and dogs up 39 weeks. The selection of species and duration of the studies are appropriate for the proposed indication. Recovery periods were included in the 13-weeks male rat study (30 days), 13-weeks male dog study (2 months) and 26 weeks female rats study (2 months) and are recommended, but missing, in pivotal toxicity studies, namely the 26 weeks in male rats and 39 weeks in dogs. The adequacy of including recovery periods in pivotal toxicity studies is supported by the detection of effects such as bile duct/oval cell hyperplasia in dogs only in the longer studies and because non-metastatic castration-resistant prostate cancer may include earlier stage prostate cancer and patient populations outside the scope of the ICH S9. However, considering apalutamide-related findings were reported to partially or fully recover in 13-weeks male rat and dog studies and the 3Rs (Replacement, Reduction and Refinement) principle, additional studies to assess the reversibility of finding in longer toxicity studies are not required. In addition, the Applicant should perform long term carcinogenicity studies, which may be useful to assess the clinical relevance of hyperplasias found in dogs.

Most toxicities affected the reproductive system, mammary glands, pituitary gland, adrenal glands, thymus, white blood cells, red cell mass, platelets, and serum cholesterol. All findings were at least partly reversible within 30 or 60 days. Plasma exposure levels of apalutamide at which these findings were observed were slightly below (male dog) or around (male rat) the apalutamide exposure in individuals with CRPC.

Additionally, hepatocellular and thyroid hypertrophy were observed in rats, and bile duct/oval cell hyperplasia was observed in the 39-week male dog study with concomitant increases in serum ALP. ALP increases (also in rats) were shown to be fully reversible, but recovery of the bile duct/oval cell hyperplasia was not assessed.

The in vitro and in vivo test were negative and apalutamide was considered no genotoxic.

According to the ICH S9 guideline, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer. However, However, clinical studies seem to indicate that the product might increase significantly the overall survival on NM-CRPC patients with high risk of developing metastasis and the ICH S1A states that in cases where the therapeutic agent is successful and life is significantly prolonged, there may be later concerns regarding secondary cancers. In addition, considering the observed hypertrophic effects caused by apalutamide in the repeat-dose toxicity studies, even though the compound is not genotoxic, carcinogenic studies should be conducted. The Applicant has planned a nonclinical carcinogenicity program with apalutamide. The final report of a 2-year carcinogenicity study in the rat will be available by the third quarter of 2021 and the final report of a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse will be available by the third quarter of 2020. The Applicant is requested for a letter of commitment to carry out carcinogenicity studies on the proposed date.

Reprotoxicity studies indicate apalutamide may impair fertility in males.

No evidences of phototoxicity has been found.

Regarding the non-clinical part of the RMP, taking into account the current version of the guideline on good pharmacovigilance practices, it is expected that drug-drug interactions could be manageable in the clinic without negatively impacting the overall benefit-risk of apalutamide. Consequently, only “seizures” is a safety concern relevant to humans.

Based on the environmental risk assessment, no adverse environmental effects are anticipated as a consequence of the use of apalutamide for the treatment of prostate cancer as indicated in the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of apalutamide were sufficiently characterised.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Phase 1 Healthy Volunteer Studies:

Study Number	Study Title	Status
ARN-509-006	14C-ARN-509 Microdose Absolute Bioavailability and Microtracer Absorption, Metabolism, and Excretion Study in Healthy Volunteers	Completed
56021927PCR1007	A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Relative Bioavailability of 7 Test Tablet Formulations of JNJ-56021927 With Respect to the Capsule Formulation of JNJ-56021927 Under Fasted Conditions in Healthy Male Subjects	Completed
56021927PCR1011	A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Relative Bioavailability of 3 Tablet Formulations of JNJ-56021927 With Respect to the Capsule Formulation of JNJ-56021927 in Healthy Male Subjects	Completed
56021927PCR1012	An Open-Label, Randomized, Parallel-Group Drug-Drug Interaction Study to Assess the Effect of Multiple Doses of Itraconazole or Gemfibrozil on the Pharmacokinetics of a Single-Dose of JNJ-56021927 in Healthy Male Subjects	Completed
56021927PCR1015	A Single-Dose, Open-Label, Randomized, Crossover Study to Evaluate the Bioavailability of JNJ-56021927 Tablet Formulation Manufactured from Different Batches of Spray-Dried Powder Varying in Particle Size Distribution in Healthy Male Subjects	Completed
56021927PCR1017	A Single-dose, Open-label, Randomized, Crossover Study to Evaluate the Bioavailability of JNJ-56021927 Spray-dried Powder Tablet Formulation from Different Manufacturing Sites in Healthy Male Subjects	Completed
56021927PCR1018	A Single-Dose, Open-Label Study to Evaluate the Pharmacokinetics of JNJ-56021927 in Subjects With Mild or Moderate Hepatic Impairment Compared With Subjects With Normal Hepatic Function	Ongoing
56021927PCR1021	A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Pharmacokinetic Profile of JNJ-56021927 When Administered as the Tablet Formulation in Healthy Male Japanese Subjects	Completed

Phase 1/2 Patient Studies:

Study Number	Study Title	Patient or Healthy Volunteer	Status
ARN-509-001	An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Advanced Castration-Resistant Prostate Cancer	Patient	Ongoing
56021927PCR1008	A Phase 1 Study of Androgen Receptor Antagonist JNJ-56021927 in Subjects with Metastatic Castration-Resistant Prostate Cancer	Japanese Patients	Ongoing
56021927PCR1010	A Drug-Drug Interaction, Safety and Efficacy Study With JNJ-56021927 (ARN-509) and Abiraterone Acetate in Subjects With Metastatic Castration-Resistant Prostate Cancer	Patient	Ongoing
56021927PCR1019	An Open-label Phase 1b QT/QTc Study of JNJ-56021927 (ARN-509) in Subjects With Castration-Resistant Prostate Cancer	Patient	Ongoing
56021927PCR1020	Drug-drug Interaction Study to Evaluate the Effect of Multiple Doses of JNJ-56021927 on the Pharmacokinetics of Multiple Cytochrome P450 and Transporter Substrates in Subjects with Castration-Resistant Prostate Cancer	Patient	Ongoing

Efficacy and safety clinical studies:

Study Number Phase	Study Design Study Population Primary Objective(s)	Treatment Regimen	Number of Subjects
ARN-509-001 **Phase 1/2**	Multicenter, first-in-human, dose-escalation, proof-of-concept study Patients with progressive advanced NM-CRPC[1] **Phase 1**: To assess the safety of apalutamide in subjects with progressive advanced CRPC, determine the MTD and/or RP2D **Phase 2**: To determine PSA response at 12 weeks per PCWG2 criteria (primary objective, all cohorts). To determine MFS[3] (a secondary objective specifically in Cohort 1: NM-CRPC)	**Phase 1**: Dose-escalation of apalutamide from 30 to 480 mg once daily continuous[4] **Phase 2:** Apalutamide 240 mg once daily continuous[4]	**Phase 1:** N=30 **Phase 2**: N=97 Cohort 1: NM-CRPC Enrolled subjects: N=51 Efficacy analysis set: N=47[6] Cohort 2: mCRPC treatment naive[7] N=25 Cohort 3: mCRPC previously treated with ZYTIGA[8] N=21

Study Number Phase	Study Design Study Population Primary Objective(s)	Treatment Regimen	Number of Subjects
ARN-509-003 **Phase 3**	Randomized (2:1), double-blind, placebo-controlled, multicenter study Patients with NM-CRPC[1] To demonstrate superiority in the MFS[2] of patients with NM-CRPC treated with apalutamide versus placebo	Apalutamide 240 mg or Placebo once daily continuous[4]	N=1,207[5] Apalutamide arm: N=806 Placebo arm: N=401

2.4.2. Pharmacokinetics

The single dose clinical pharmacology program was performed in healthy male volunteers, whereas the multiple dose studies were done in prostate cancer patients.

At steady state, mean (CV%) Cmax and AUC values for apalutamide were 6 µg/mL (28%) and 100 µg.h/mL (32%), respectively.

One of the two main plasma metabolites, N-desmethyl apalutamide (JNJ-56142060), has approximately one-third the potency of apalutamide (the parent compound) and has a higher plasma AUC (AUC metabolite/parent drug ratio for N-desmethyl apalutamide following repeat-dose administration was about 1.3 (21%)) and lower protein binding than apalutamide itself (96% versus 95%), and is thus expected to contribute substantially to drug effect (about 28% to 32% of the clinical activity of apalutamide).

Absorption

Oral absorption of apalutamide is fast with Cmax 3-5 hours post dose for tablets. Absorption of apalutamide is high based oral bioavailability study 006 (after dose normalization to 240 mg, Fabs=1.1 and ranged from 1.08 to 1.13 between subjects).

The in vitro permeability of MDV3100 is high (Papp A-to-B of 42.3×10-6 cm/s), and in the mass balance study, 64.6% of the dose was recovered in urine and 22.8% of the dose as metabolites in faeces, indicating a high extent of absorption. Together with low aqueous solubility (0.001 g/100 mL or 2.5 mg/250 mL), apalutamide can be considered a BCS class II substance.

Drug transporter studies indicated that apalutamide and N-desmethyl apalutamide are substrates of P-gp but not substrates of BCRP, OATP1B1, or OATP1B3.

BIOEQUIVALENCE

Two different formulations (softgel capsules and tablets) have been used over the course of clinical development of apalutamide. Apalutamide is supplied as film coated tablet. Early clinical pharmacology and clinical studies used liquid-filled soft gelatin capsules containing a non-aqueous lipid-based solution of apalutamide.

The final selected tablet formulation had comparable bioavailability relative to the capsule formulation based on AUC∞ but resulted in slightly lower Cmax after single dose administration (N=15), with GMR (90% CI) of 107.20% (94.46-121.67%) and 90.10% (79.15-102.56%), respectively (Study 1011).

Table 5. Effect of Treatment on the Comparative Bioavailability of Apalutamide Under Fasted Conditions (Study 1011)

Parameter (Unit)	Treatment Group [a]	N	Geometric Mean	GMR Test/Reference (%)	90% CI (%)	Total CV (%)
C_{max} (µg/mL)	A	15	2.66			21.5%
	B	15	2.40	90.10	(79.15, 102.56)	
	C	15	2.26	84.90	(74.59, 96.65)	
	D	15	2.54	95.61	(83.99, 108.83)	
AUC_{last} (µg.h/mL)	A	15	198.17			21.7%
	B	15	213.52	107.75	(94.51, 122.84)	
	C	15	210.94	106.45	(93.37, 121.36)	
	D	15	197.51	99.67	(87.43, 113.63)	
AUC_{∞} (µg.h/mL)	A	15	207.99			21.0%
	B	15	222.98	107.20	(94.46, 121.67)	
	C	15	221.48	106.49	(93.82, 120.86)	
	D	15	207.40	99.72	(87.86, 113.18)	

[a] A: 240 mg given as 8x30 mg softgel capsules
B: 240 mg dose given as 4x60 mg SDP (HPMC-AS ratio 1:3) tablets
C: 240 mg dose given as 4x60 mg HME (HPMC-AS ratio 1:3) tablets
D: 240 mg dose given as 4x60 mg SDP (Eudragit ratio 1:2) tablets
Treatment A was used as the reference treatment.

Following repeat dose administrations in subjects with mCRPC (n=4), the tablet versus capsule GMRs were 92.05% for Cmax (90% CI: 66.66-127.12%) and 94.30% for AUC0-24 (90% CI: 82.19-108.20%) (Substudy 1010). The GMR for Cmax was consistent with that derived from the bioequivalence simulation analysis.

The formulations are not strictly bioequivalent according to the criteria outlined in the Bioequivalence guideline. As mentioned in the scientific advice, these criteria have, however, been set with generic applications in mind, where the generic product is approved solely on bioequivalence data and therefore must be shown to be essentially similar to the originator. For a change of formulation during the development of an originator product, other considerations may be taken into account. The pivotal study was conducted with both

formulations and an assessment about the effect on efficacy and safety has been conducted. Highlighting that apparently less diarrhea and nauseas events have been observed with tablets Differences on Cmax of approximately 10% are initially acceptable. This differences could have certain impact on studies where food effect or DDI effects are being studies. A specific substudy on food effect was conducted with tablets in study 1011, which is reassuring. Although certain impact on DDI studies cannot be fully ruled out, the impact is not expected to be meaningful

Note: The following studies were conducted using a 30-mg softgel capsule: the absolute bioavailability/mass balance study (Study 006) and the drug-drug interaction study on effect of strong CYP3A4 and CYP2C8 on apalutamide (Study 1012). All ongoing subjects receiving capsules in Studies 001 (the first-in-man Phase 1/2 study), 1008 (the PK study in Japanese subjects with mCRPC), Study 1010 (DDI study on effect of apalutamide on abiraterone and prednisone), and the Phase 3 SPARTAN (Study 003) were switched to tablets. Studies 1018 (Hepatic impairment), 1019 (QT prolongation), 1020 (DDI study on Effect of apalutamide on other drug), and 1021 (Japanese) were conducted using the tablet formulation only.

To support the manufacturing and control strategies of the proposed commercial tablet formulation, 2 additional relative bioavailability studies were conducted. The effect of CQAs of the intermediate on the bioavailability of the tablet formulation was investigated in Study 1015. The bioavailability of the tablet formulation produced from 2 different manufacturing sites was assessed in Study 1017. Results of those studies showed that formulations were bioequivalent according to the criteria outlined in the Bioequivalence guideline.

Food-effect

Two substudies to investigate food effect were conducted; one with capsules (substudy 1001) and other with tablets (substudy 1011). As only tablets formulation will be commercialized, main attention is paid to substudy 1011.

Food effect substudy in study 1011 has a parallel-group design with apparently similar demographic and baseline characteristics between arms. Considering the long half-life of apalutamide the parallel-group design is acceptable. This food effect study conducted in healthy subjects under fasting conditions and with a high-fat meal indicated that Cmax was decreased by 16% (83.95; 90% CI: 74.90, 94.11) while AUC remained unchanged (94.08; 90% CI: 83.75, 105.70). Median tmax was delayed about 2 hours with food (from 3 hours to 5 hours). The decrease in Cmax was not considered clinically relevant. Additionally, apalutamide was administered without regard to food in pivotal study.

Table 6. Effect of Food on the Comparative Bioavailability of Apalutamide (Study 1011)

Parameter (Unit)	Treatment Group [a]	N	Geometric Mean	GMR Test/Reference (%)	90% CI (%)	Total CV (%)
C_{max}	B	15	2.40			18.5%
(µg/mL)	E	15	2.01	83.95	(74.90, 94.11)	
AUC_{last}	B	15	213.52			19.6%
(µg.h/mL)	E	15	206.53	96.73	(85.76, 109.10)	
AUC_{∞}	B	15	222.98			18.5%
(µg.h/mL)	E	14	209.78	94.08	(83.75, 105.70)	

[a] B: 240 mg dose given as 4x60 mg SDP (HPMC-AS ratio 1:3) tablets under fasted conditions
E: 240 mg dose given as 4x60 mg SDP (HPMC-AS ratio 1:3) tablets under fed condition
Treatment B was used as the reference group.

Distribution

Mean V/F in the single dose study in healthy male subjects ranged between 250 and 296 L. Based on the population PK analysis the Vss was estimated to be 276 L in subjects with CRPC after oral multiple dose administration. Overall, the volume of distribution of apalutamide was greater than the volume of total body water, indicative of extensive extravascular distribution.

In vitro data show high protein binding of both apalutamide (96%) and major plasma metabolite (N-desmethyl metabolite 95%). Main bound is to serum albumin with no concentration dependency. This needs to be considered when discussing the effects of drug-drug interactions or impaired organ function on active moiety (apalutamide+ N-desmethyl metabolite).

The mean blood-to-plasma ratios of total 14C-radioactivity ranged from 0.91 to 0.98, indicating equal distribution of total 14C-radioactivity between plasma and red blood cells (Study 006).

Metabolism

In the mass-balance study after a single dose of apalutamide, in parallel to parent drug (45% of total radioactivity AUC) two major plasma metabolites were identified, N-desmethyl metabolite (44% of total AUC) and inactive carboxylic acid metabolite (3% of total AUC). As apalutamide and the two metabolites together constituted more than 90% of total radioactivity AUC, and no unidentified metabolites were found, it seems unlikely that there would be other quantitatively or pharmacologically/toxicologically important plasma metabolites.

In vitro studies indicate that apalutamide is metabolized primarily by cytochrome P450 (CYP) 2C8 and CYP3A4 to form N-desmethyl apalutamide. N-desmethyl apalutamide is further metabolized to the inactive carboxylic acid metabolite, JNJ-56142021, by carboxylesterase. The importance of CYP2C8, and to a lower extent CYP3A4, was verified in vivo in interaction studies with the CYP2C8 inhibitor gemfibrozil (68% increase in apalutamide AUC, 15.2% decrease in N-desmethyl apalutamide and 102% increase in inactive carboxylic acid metabolite AUC) and the CYP3A4 inhibitor itraconazol (1% increase in apalutamide AUC, 12% increase in N-desmethyl apalutamide and 44% increase in inactive carboxylic acid metabolite AUC). Based on a PBPK model the contribution of CYP2C8 seems to decrease over time from 58% at single-dose to 40% at steady state whereas the contribution of CYP3A4 seems to increase from 13% at single-dose to 37% at steady state. However, this PBPK model can only be considered as an exploratory model. Thus, firm conclusion from it should not be reached and results should be interpreted with caution. In general, the metabolism of apalutamide and its active metabolite, N-desmethyl apalutamide, is sufficiently characterized.

Figure 2. Proposed In Vivo Metabolic Pathways for Apalutamide in Human Subjects

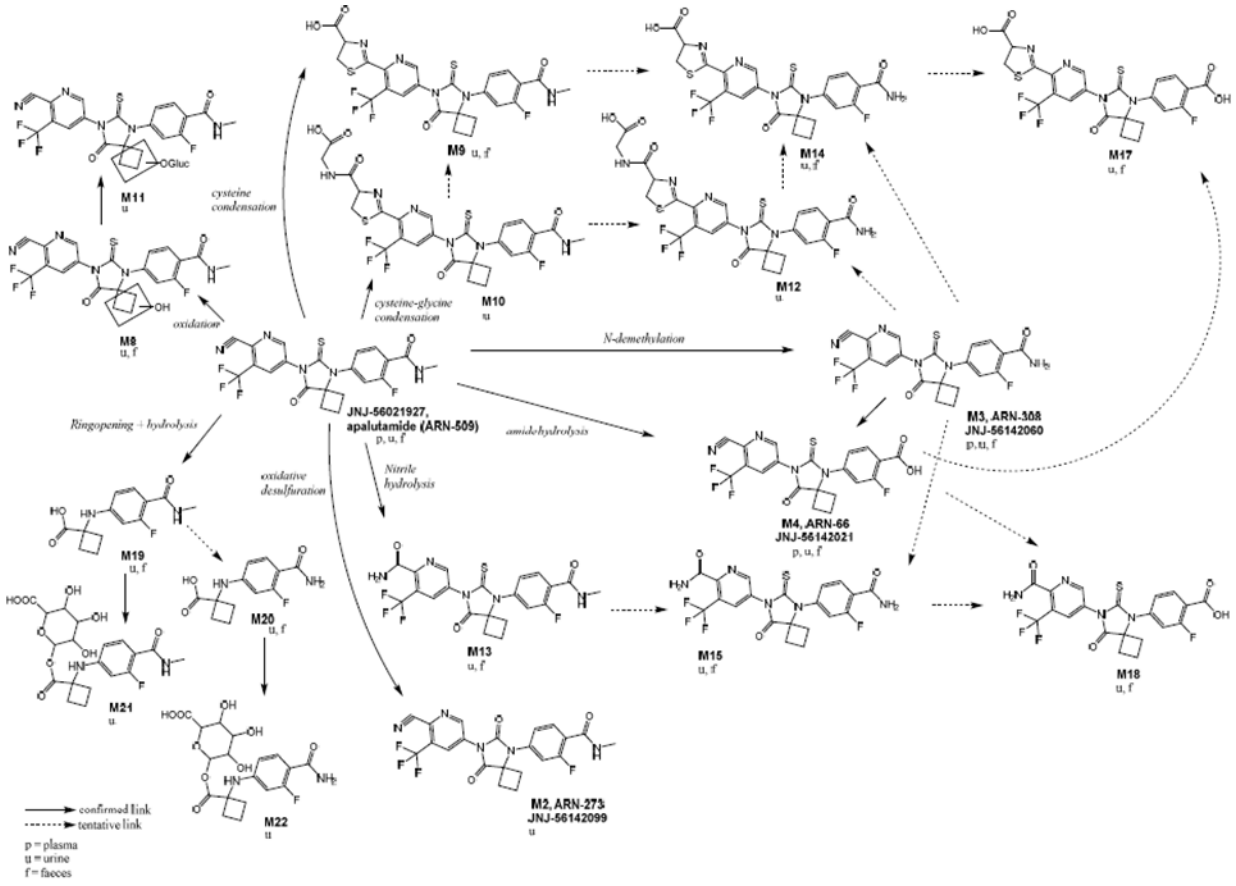
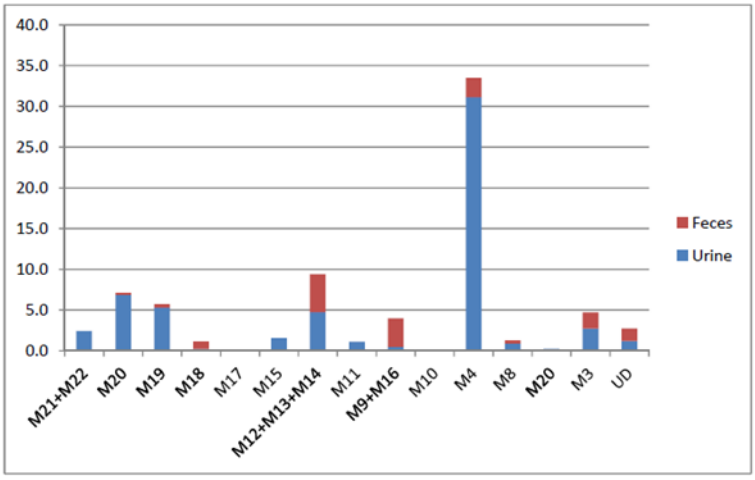


Table 7. Mass balance of unchanged 14C-JNJ-56021927 and its metabolites (expressed as % of the administered dose) in human urine+feces following oral administration of JNJ-56021927 at 240 mg

Male Human - Urine + Faeces					
	0-240 h		240-1680 h		0-1680 h
Component	%Inj	%Dose	%Inj	%Dose	%Dose
M21+M22	3.2	0.91	4.2	1.53	2.44
M20	9.2	2.28	14.0	4.85	7.14
M19	14.2	3.49	6.9	2.22	5.71
M18	4.7	0.47	3.9	0.70	1.17
M17	trace	trace	trace	trace	trace
M15	3.0	0.8	2.0	0.7	1.54
M12+M13+M14	19.5	3.22	30.0	6.17	9.40
M11	2.4	0.66	1.2	0.45	1.11
M9+M16	21.5	1.91	12.2	2.09	4.00
M10	trace	trace	trace	trace	trace
M4	53.3	13.22	61.9	20.29	33.50
M8	4.7	0.80	2.0	0.48	1.29
M2	0.6	0.17	0.2	0.07	0.23
M3	11.4	1.60	13.2	3.10	4.70
UD	14.8	1.82	4.7	0.92	2.74
Sum of reported entities		31.4		43.4	74.8
Sum observed metabolites (dose %)		36.0		52.3	88.3

Figure 3.Mass Balance bargraph: metabolite abundance in feces and urine expressed as % of the dose



The potential impact of CYP2C8 polymorphism on apalutamide pharmacokinetic have been discussed by the applicant. Genetic polymorphism is not expected to have a clinically meaningful impact on PK of apalutamide and N-desmethyl apalutamide. However, particular attention was suggested to interaction with CYP3A4 inhibitors in CYP2C8 poor metabolisers. However, after this issue was properly disused by the applicant, it was accepted that the interaction of apalutamide with CYP3A4 inhibitors in CYP2C8 poor metabolisers is expected to be similar as in other genotypes.

Elimination

Apalutamide is mainly hepatically eliminated, and renal excretion of unchanged drug is low (1.2% of dose). Apalutamide showed an oral clearance of 1.31 L/h after single dosing, increasing to 2.04 L/h at steady state as results of auto-induction. Mean terminal half-life in patients at steady state is 3 days. With daily administration, apalutamide accumulates approximately 5-fold.

The metabolites of apalutamide are excreted mainly in urine, and the most abundant metabolites in urine are M4 (31% of dose) followed by M20 (approximately 7% of dose). No relevant biliary excretion seems to occur. The recovery in the mass balance study (89%) was somewhat low, but acceptable in view of the long half-life and the long sampling period in the study (up to 70 days post-dose), and more than 80% of the recovered radioactivity was identified.

Dose proportionality and time dependencies

Following single and repeat once daily dosing, apalutamide exposure (Cmax and AUC) increased in a dose-proportional manner across the dose range of 30 to 480 mg. Following multiple dose administration of 240-, 300-, 390-, and 480-mg apalutamide, N-desmethyl apalutamide Cmax and AUC also increased with increasing dose. Statistical analysis of dose proportionality of N-desmethyl apalutamide PK was not performed due to the limited amount of data.

An increase in apparent clearance (CL/F) was observed with repeat dosing, likely due to induction of apalutamide's own metabolism. Apalutamide is a strong inducer of CYP3A4. With a once daily dosing regimen, apalutamide steady state was achieved after 4 weeks (Study 001) and the mean accumulation ratio was approximately 5-fold based AUC (Study 1019). The metabolism of N-desmethyl apalutamide was not

time-dependent. The mean EHL for apalutamide in subjects with CRPC was about 78.7 hours (approximately 3 days) at steady-state, indicating that accumulation was less than expected based on the mean t1/2 of 183 hours after single-dose. The Applicant was asked to discuss the implications of accumulation after multiple dosing on possible higher incidence of adverse events that could arise with this enhanced exposure. After applicant's deeply discussion, this issue was considered resolved since most subjects were already at steady state concentration levels when they suffer from the TEAE and the higher frequency of TEAEs with continued dosing was not observed.

Intra-and inter-individual variability

PK of apalutamide is characterized by low to moderate intrasubject and intersubject variability (<30%). In the population PK analysis, the intersubject variability for N-desmethyl apalutamide was estimated to be low (19.7%, 19.7%, and 19.6% for AUC0-24,ss, Cmin, and Cmax, respectively).

Pharmacokinetics in target population

All clinical studies were conducted in adult male subjects only. Single-dose studies were conducted in healthy male subjects because the effect of androgen blockade after single-dose administration was limited in duration. However, multiple-dose studies only enrolled subjects with prostate cancer as prolonged androgen suppression in healthy subjects was not recommended. Using single and repeat dose data, the population PK analysis identified that healthy subjects had a 27% higher relative bioavailability compared to subjects with CRPC, resulting in proportionally higher AUC0-24,ss of apalutamide and N-desmethyl apalutamide. It should be noted that when health status is evaluated as a covariate GMR resulted in 1.42 (90%CI: 1.36, 1.49) for apalutamide and 1.29 (90% CI: 1.25, 1.33) for N-desmethyl apalutamide. The potential impact of this differences observed on PK between healthy subjects and cancer patients on extrapolation the results of studies conducted on healthy patients to cancer patients, specially study on hepatic impairment and on DDI with strong CYP3A4 and CYP2C8 inhibitors was requested to be discussed. It was accepted that in the PK analysis other confounded factors could have impact on results, while data obtained at single dose under controlled conditions seems to be in line between healthy subjects and patients. Thus, this issue was considered resolved.

Data from the following 7 clinical studies were pooled for the population PK analysis: 001, 1008 (Japanese), 1011 (bioequivalence among different formulations), 1018 (hepatic impairment), 1019 (QT prolongation), 1021 (Japanese), and 003 [SPARTAN] (pivotal).

Table 8. Population PK parameter estimates (RSE, %) for the base, reference and final population PK model for apalutamide and JNJ-56142060

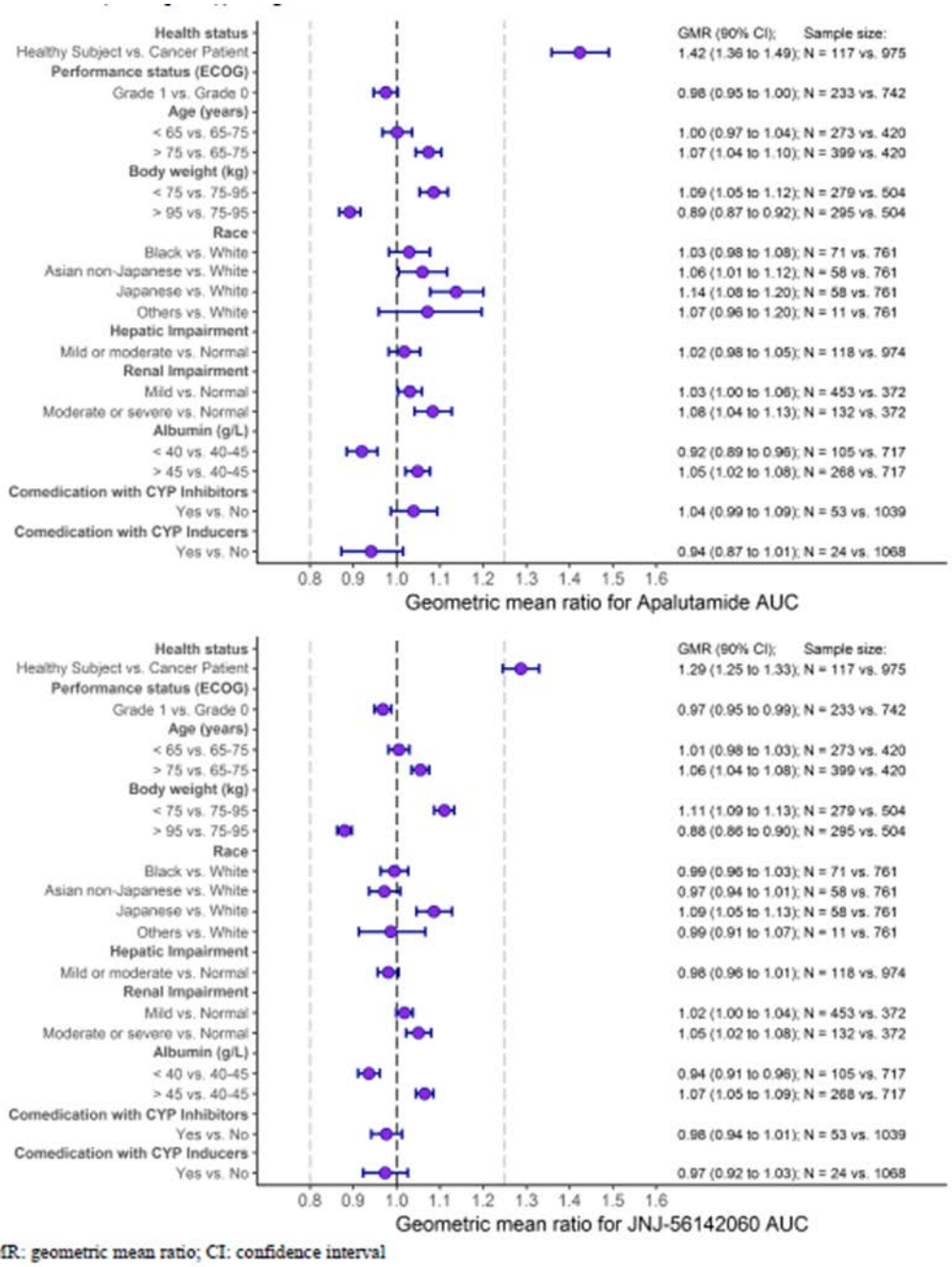
Pharmacokinetic Parameters[a]	Reference Model (Dataset A; Run003.mod)	Reference Model (Dataset C; Run004.mod)	Final Model (Dataset C; Run041.mod)
	Estimate (RSE%)	Estimate (RSE%)	Estimate (RSE%)
Apalutamide			
t_{lag} (h)	0.417 (0.3)	0.417 (0.3)	0.418 (0.3)
$k_{a,tablet}$ (1/h)	0.223 (7.0)	0.212 (6.8)	0.216 (6.7)
$\Theta_{capsule}$ [b]	0.977 (9.8)	0.861 (8.8)	0.851 (8.6)
V_c/F (L)	16.1 (11.6)	16.4 (10.7)	14.5 (9.7)
CL_{ni}/F (L/h)	1.10 (5.4)	1.16 (3.8)	1.17 (4.4)
CL_{i0}/F (L/h)	0.222 (22.1)	0.182 (20.9)	0.141 (35.2)
CL_{ins}/F (L/h)	0.904 (6.0)	0.972 (4.6)	0.869 (6.0)
k_{enz} (1/h)	0.0015 (6.3)	0.0016 (4.1)	0.0016 (4.0)
t_{enz} (h)	49.5 (22.6)	57.7 (20.6)	57.7 (fixed)
V_p/F (L)	313 (4.3)	299 (4.5)	261 (4.3)
Θ_{WT} [c]	-	-	0.882 (12.7)
Q/F (L/h)	21.2 (4.2)	22.9 (3.5)	22.6 (3.5)
F_{CRPC} [f]	-	1 (fixed)	1 (fixed)
Θ_{weight} [d]	-	-	-0.519 (5.2)
$\Theta_{Albumin}$ [d]	-	-	0.545 (13.0)
$\Theta_{healthy\ subjects}$ [d]	-	-	0.27 (10.6)
JNJ-56142060			
V_{cm}/F (L)	26.9 (7.3)	26.3 (7.1)	26.3 (6.9)
CL_m/F (L/h)	1.51 (1.9)	1.6 (0.8)	1.53 (0.8)
V_{pm}/F (L)	242 (3.9)	223 (4.6)	212 (4.6)
$Q_{m,CRPC}/F$ (L/h)	50.5 (5.0)	53.1 (4.4)	67.3 (4.8)
$\Theta_{healthy\ subjects}$ [e,f]	-	-	-0.355 (10.7)
Inter-individual variability (CV %)			
Apalutamide			
ω k_a	47.3 (16.8)	59.0 (12.4)	60.7 (11.8)
ω V_c	231.5 (12.5)	230.1 (14.6)	230.1 (14.9)
ω CL	23.8 (9.2)	19.1 (5.3)	19.1 (4.8)
ω V_p	37.1 (13.5)	54.5 (8.5)	46.1 (8.1)
ω Q	34.1 (15.8)	35.2 (15.9)	34.6 (17.0)
ω F	26.5 (6.7)	22.7 (4.7)	15.0 (4.6)
JNJ-56142060			
ω V_{cm}	56.8 (23.0)	58.2 (23.9)	56.8 (25.3)
ω CL_m	8.3 (41.1)	4.6 (52.1)	7.3 (16.2)
ω V_{pm}	32.8 (14.1)	47.1 (10.2)	47.3 (10.9)
ω Q_m	30.6 (19.1)	31.0 (10.2)	22.6 (29.2)
Residual variability (CV %)			
σ_1 (Apalutamide)	22.4 (0.4)	22.6 (0.3)	22.6 (0.3)
σ_2 (JNJ-56142060)	13.7 (0.3)	14.9 (0.2)	15.0 (0.2)
Objection function value	-21334.332	-31011.378	-31703.204

RSE, relative standard error; CV, coefficient of variation; t_{lag} is the lag-time after which apalutamide absorption begins; $k_{a,tablet}$, apalutamide apparent first-order absorption rate constant for tablet formulation; *capsule* is the formulation effect of apalutamide capsule being $k_{a,capsule} = k_{a,tablet}/F \times \Theta_{capsule}$; V_c/F, apalutamide apparent volume of distribution of the central compartment; CL_{ni}/F, apalutamide apparent not inducible clearance; CL_{i0}/F, apalutamide apparent inducible clearance at baseline; CL_{ins}/F, apalutamide apparent induced clearance at steady state; CL, apalutamide total clearance; k_{enz}, enzyme inducible first-order turnover rate; t_{enz}, lag time after which the induction begins; V_p/F, apalutamide apparent volume of distribution of the peripheral compartment; Q/F, apalutamide apparent inter-compartmental clearance; V_{cm}/F, JNJ-56142060 apparent volume of distribution; CL_m/F, JNJ-56142060 apparent clearance; V_{pm}/F, JNJ-56142060 apparent volume of distribution of the peripheral compartment; Q_m/F, JNJ-56142060 apparent inter-compartmental clearance; F, relative bioavailability. [a]Typical PK parameters reported are apparent since the absolute bioavailability and the fraction of apalutamide converted to JNJ-56142060 are unknown and not estimable from the available datasets. [b]$k_{a,capsule} = k_{a,tablet} \times \Theta_{capsule}$. [c] $V_p/F = \Theta_{VPF} \times (WT/75)^{\Theta WT}$. [d]$F = 1 \times (AGE/75)^{\Theta WT} \times (WT/75)^{\Theta WT} \times (ALB/44)^{\Theta WT} \times (1+\Theta_{HEALTH})$. [e] $Q_m/F = \Theta_{Qm/F} \times (1+\Theta_{healthy\ subjects})$. [f]CRPC castrate resistant prostate cancer subjects

The following covariates, health status, weight and serum albumin concentration, were statistically associated with apalutamide or JNJ-56142060 exposure. Nevertheless, the magnitude of the effect of body weight and serum albumin concentration on the apalutamide or JNJ-56142060 pharmacokinetic parameters is low (<25%). Age, race (categorized as Black, White, Asian non-Japanese, Japanese and Other), renal function, hepatic function, TB, AST, ALT, ALP, TP, eGFR, CYP3A4-inducing and CYP2C8-inhibiting co-medication had no

discernible impact on the pharmacokinetic parameters of apalutamide and JNJ-56142060. Consequently, apalutamide dose adjustment based on these covariates is not warranted.

Figure 4.Forest plot for the covariate evaluation for Apalutamide (upper panel) and JNJ-56142060 (lower panel), using Dataset C.



GMR: geometric mean ratio; CI: confidence interval

In the final model all parameters were estimated with acceptable precision with a RSE <35.2% for the fixed effects and RSE<30% for the random effects. The residual error was 22.6% for apalutamide and 14.9% for JNJ-56142060. The goodness-of-fit plots of the final model for apalutamide and JNJ-56142060 against the population model prediction and individual model prediction seems to show a normal random scatter around the identity line. However, a slight over prediction trend seems to be observed with low concentrations, especially

for apalutamide. The distribution of conditional weighted residuals and normalized prediction distribution errors (NPDE), as a function of the population predictions and time, supported adequacy of the model, although the same slight trend to over prediction with low concentrations is observed in those plots. The prediction corrected VPC shows that the final model described well the time course of both apalutamide and JNJ-56142060 plasma concentrations following single and multiple dose administrations, although the variability predicted during the first weeks since the first dose at single dose is higher than the observed one. The general trend in the data can be considered well captured by the population PK model.

Special populations

No clinically relevant effects of renal function [patients with mild (n=453) and moderate (n=132) renal impairment or renal normal function (n=372)], hepatic function [patients with mild hepatic impairment (n=118) or hepatic normal function (n=974)] , race [White (n=761), Black (n=71), Asian non-Japanese (n=58), Japanese (n=58), other (n=11)] or age (range: 18-94 years), TB, AST, ALT, ALP, TP, eGFR, CYP3A4-inducing and CYP2C8-inhibiting co-medication on apalutamide or N-desmethyl apalutamide clearances were observed in the population PK model.

The following covariates, health status, weight and serum albumin concentration, were statistically associated with apalutamide or JNJ-56142060 exposure. Nevertheless, the magnitude of the effect of body weight and serum albumin concentration on the apalutamide or JNJ-56142060 pharmacokinetic parameters is low (<25%). Health status has been discussed above (PK in target population).

A single dose clinical study was performed in patients with mild and moderate hepatic impairment, showing no clinically relevant effects of hepatic function on apalutamide pharmacokinetics [AUC∞ GMRs; 90% CI for apalutamide of mild vs normal: 94.59% (76.06, 117.64) and moderate vs normal 113.35% (81.70, 157.26), AUC∞ GMRs; 90% CI for N-desmethyl apalutamide of mild vs normal: 96.28% (83.79, 110.62) and moderate vs normal 81.15% (65.00, 101.32)]. No dose adjustments are proposed in the SmPC for these groups. In the mild hepatic impairment group, 7 subjects out of 8 have normal levels of serum albumin, serum bilirubin and prothrombin time. In the moderate group, 4 out of 8 patients have normal levels of serum albumin, serum bilirubin and prothrombin time. Median Child-Plug Score in mild group is 5 and 7.5 in moderate group. It should be noted that even when differences on patients with mild or moderate hepatic impairment in comparison with patients with normal hepatic function do not seem to be relevant at single dose, their relevance at steady state cannot be fully ruled out due to the time-dependent PK exhibit by apalutamide. Additionally, safety data on patients with moderate hepatic impairment are limited to a single dose study (only 2 patients with hepatic impairment were included in the pivotal study). For all the above, no dose adjustments recommendations are accepted for patients with mild and moderate hepatic impairment based on results at singe dose. However, a Phase I, single dose, clinical PK study in healthy non-cancer subjects with normal hepatic function and non-cancer subjects with severe hepatic impairment is required (see RMP). Meanwhile further information is not available on patients with severe impairment, apalutamide is not recommended in this population (see SmPC).

Table 9. Geometric Mean Ratios and Their Associated 90% CIs for Total Apalutamide Following Single-Dose Administration of 240 mg Apalutamide in Subjects With Normal or Impaired Hepatic Function (Study 1018)

Parameter (Unit)	Geometric Mean: Hepatic Impairment (Test) N=8	Geometric Mean: Normal Hepatic Function (Reference) N=8	GMR, % (90% CI)
Mild Hepatic Impairment			
C_{max} (µg/mL)	1.94	1.91	101.66 (77.07, 134.09)
AUC_{last} (µg/mL)	178	190	93.52 (74.82, 116.90)
AUC_{∞} (µg.h/mL)	189	200	94.59 (76.06, 117.64)
Moderate Hepatic Impairment			
C_{max} (µg/mL)	1.99	1.91	104.21 (74.01, 146.71)
AUC_{last} (µg/mL)	206	190	108.72 (78.87, 149.89)
AUC_{∞} (µg.h/mL)	226	200	113.35 (81.70, 157.26)

N = maximum number of subjects with data.

Table 10. Geometric Mean Ratios and Their Associated 90% CIs for Total Apalutamide Metabolite N-Desmethyl Apalutamide Following Single-Dose Administration of 240 mg Apalutamide in Subjects With Normal or Impaired Hepatic Function (Study 1018)

Parameter (Unit)	Geometric Mean: Hepatic Impairment (Test) N=8	Geometric Mean: Normal Hepatic Function (Reference) N=8	GMR, % (90% CI)
Mild Hepatic Impairment			
C_{max} (µg/mL)	0.267	0.271	98.85 (72.90, 134.03)
AUC_{last} (µg/m)L	156	165	94.74 (80.74, 111.18)
AUC_{∞} (µg.h/mL)	171	177	96.28 (83.79, 110.62)
Moderate Hepatic Impairment			
C_{max} (µg/mL)	0.199	0.271	73.48 (50.43, 107.06)
AUC_{last} (µg/mL)	124	165	75.32 (60.21, 94.21)
AUC_{∞} (µg.h/mL)	144	177	81.15 (65.00, 101.32)

N = maximum number of subjects with data.

No data is available in patients with severe renal impairment. Administration with caution was recommended in this population in the SmPC, considering the low renal excretion of apalutamide and the fact that this recommendation is in line with enzalutamide.

Elderly population is considered properly represented in those studies. Age of studied population is in line with age on patients with the study disease.

Pharmacokinetic interaction studies

Effects of other substances on apalutamide:

Medicines that inhibit CYP2C8

In a drug-drug interaction study, the C_{max} of apalutamide decreased by 21% while AUC increased by 68% following co-administration of apalutamide 240 mg single dose with gemfibrozil (strong CYP2C8 inhibitor). As the active metabolite decreased (15.2% in AUC), the effect on active moiety (apalutamide+ N-desmethyl apalutamide) was substantially smaller (44.5% increase in AUC). Due to time-dependent pharmacokinetic of apalutamide, data on steady state are relevant. Simulations using a PBPK model 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 unbound apalutamide plus the potency-adjusted unbound active metabolite), the steady-state C_{max} and AUC may increase by 19% and 23%, respectively.

Table 11. Effect of CYP2C8 Inhibitor – Gemfibrozil

Effect of CYP2C8 Inhibitor - Gemfibrozil				
Parameter (Unit)	**Geometric Mean**		**GM Ratio**	**90% CI**
	Apalutamide + Gemfibrozil	**Apalutamide**		
Apalutamide				
AUC0-inf (µg*h/mL)	381.98	227.92	167.60	149.05-188.45
Cmax (µg/mL)	2.65	3.35	79.09	71.60-87.37
JNJ-56142060 (Active metabolite)				
AUC0-inf (µg*h/mL)	174.68	205.98	84.80	76.62-93.86
Cmax (µg/mL)	0.18	0.34	54.94	45.67-66.10
JNJ-56142021 (Inactive metabolite)				
AUClast (µg*h/mL)	7.48	3.70	202.29	94.51-432.97
Cmax (µg/mL)	0.08	0.06	144.51	127.90-163.27
Sum JNJ-56021927 + JNJ-56142060				
AUC0-inf (µg*h/mL)	429.92	297.43	144.54	130.56-160.02
Cmax (µg/mL)	2.74	3.47	78.95	71.42-87.27

Current recommendations with strong, moderate and mild CYP2C8 inhibitor seem to be reasonable:

"No initial dose adjustment is necessary when Erleada is co-administered with a strong inhibitor of CYP2C8 (e.g., gemfibrozil, clopidogrel) however, consider reducing the Erleada dose based on tolerability (see section 4.2). Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide".

Medicines that inhibit CYP3A4

In a drug-drug interaction study, the Cmax of apalutamide decreased by 22% while AUC was similar following co-administration of Erleada as a 240 mg single dose with itraconazole (strong CYP3A4 inhibitor). The effect on active moiety (apalutamide+ N-desmethyl apalutamide) was substantially smaller (4% increase in AUC). Due to time-dependent pharmacokinetic of apalutamide, data on steady state are relevant. Simulations using a PBPK model suggest that ketoconazole (strong CYP3A4 inhibitor) may increase the steady-state Cmax and AUC of apalutamide by 38% and 51%, respectively. For the active moieties, the steady-state Cmax and AUC may increase by 23% and 28%, respectively.

Table 12. Effect of CYP3A4 Inhibitor – Itraconazole

Effect of CYP3A4 Inhibitor - Itraconazole				
Parameter (Unit)	**Geometric Mean**		**GM Ratio**	**90% CI**
	Apalutamide + Itraconacolel	**Apalutamide**		
Apalutamide				
AUC0-inf (µg*h/mL)	230.66	227.92	101.20	90.19-113.56
Cmax (µg/mL)	2.62	3.35	78.29	70.87-86.48
JNJ-56142060 (Active metabolite)				
AUC0-inf (µg*h/mL)	230.78	205.98	112.04	101.81-123.29
Cmax (µg/mL)	0.28	0.34	84.83	70.73-101.73
JNJ-56142021 (Inactive metabolite)				
AUClast (µg*h/mL)	5.33	3.70	144.27	68.30-304.73
Cmax (µg/mL)	0.05	0.06	94.99	84.25-107.10
Sum JNJ-56021927 + JNJ-56142060				
AUC0-inf (µg*h/mL)	309.11	297.43	103.93	94.42-114.39
Cmax (µg/mL)	2.72	3.47	78.44	71.09-86.56

Current recommendations with strong, moderate and mild CYP3A4 inhibitor seem to be reasonable:

"No initial dose adjustment is necessary when Erleada is co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole, ritonavir) however, consider reducing the Erleada dose based on tolerability (see section 4.2). Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide".

Medicines that induce CYP3A4 or CYP2C8

The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated in vivo. Simulations using a PBPK suggested that rifampicin (strong CYP3A4 and moderate CYP2C8 inducer) may decrease the steady-state Cmax and AUC0-24 of apalutamide by 25% and 34%, respectively. For the active moieties, the steady-state Cmax and AUC0-24 may decrease by 15% and 19%, respectively. As mentioned above, data of PBPK model for steady-state are reassuring but this PBPK model has several limitations that preclude reaching firm conclusion from it (see above)**.** The applicant justifies that a drug interaction study to evaluate the effects of rifampicin on steady-state PK of apalutamide was deemed infeasible due to safety and ethical concerns as it would require prolonged administration (>28 days) of rifampicin to cancer patients to reach new steady state of apalutamide given its long half-life. However, a similar DDI study was conducted for enzalutamide resulting in a 37% decrease of AUC. This results seems to be in line with simulation results. However, it should be noted that half-life of apalutamida is shorter than enzalutamide. The applicant provided a reasonable justification on the infeasibility of conducting an in vivo DDI study on effect of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide.

Other medicines

As apalutamide is not ionizable under relevant physiological pH conditions, acid lowering agents are not expected to affect the solubility and bioavailability of apalutamide.

In vitro, apalutamide and its N-desmethyl metabolite are substrates for P-gp. However, as apalutamide is completely absorbed after oral administration, P-gp is not expected to limit the absorption of apalutamide. Inhibition or induction of P-gp is not expected to change the PK of apalutamide in a clinically relevant manner.

Effects of apalutamide on other substances:

In vitro studies showed that apalutamide and N-desmethyl apalutamide are most active as CYP3A4 inducers, are moderate inhibitors of CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4 at clinically relevant concentrations. The induction of CYP3A4 suggested that apalutamide might induce other CYP isozymes and drug transporters (eg, CYP2C family and MDR1/P-gp) via activation of pregnane X receptor. In vitro data also indicated that apalutamide might be a clinically relevant inhibitor of P-gp and BCRP. Apalutamide and N-desmethyl apalutamide are shown to inhibit OATP1B1 and OATP1B3 in vitro. However, the potential to affect substrates of these transporters is not expected to be clinically relevant.

The significance of these in vitro findings was evaluated in a clinical "cocktail" drug-drug interaction study that included drug probes for CYP3A4 (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), CYP2C8 (pioglitazone), P-gp (fexofenadine), and BCRP/ OATP1B1 (rosuvastatin) (Study 1020).

The results of this study suggest that apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9, P-gp, BCRP and OATP1B1. 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), a 30% decrease in the AUC of fexofenadine (P-gp substrate) and a 41% decrease in the AUC of rosuvastatin (BCRP/OATP1B1 substrate) was observed. Apalutamide did not cause clinically meaningful changes in exposure of piglitiazone (CYP2C8 substrate).

Table 13. Results of cocktail study (1020)

Analyte	PK Parameter	n	Geometric Mean		Geometric Mean Ratio, (%)	90% CI, (%)
			Drug Probe alone (reference)	Drug Probe + Apalutamide (test)		
Midazolam (CYP3A4)	C_{max}, ng/mL	21	7.25	1.68	23.16	17.88 - 29.98
	AUC_{last}, ng.h/mL	21	37.8	3.14	8.30	6.06 - 11.37
	AUC_{∞}, ng.h/mL	17	41.7	3.38	8.11	5.86 - 11.22
S-Warfarin (CYP2C9)	C_{max}, ng/mL	21	419	350	83.51	76.53 - 91.14
	AUC_{last}, ng.h/mL	21	16272	8815	54.17	50.36 - 58.28
	AUC_{∞}, ng.h/mL	12	17823	9169	51.45	46.76 - 56.61
Omeprazole (CYP2C19)	C_{max}, ng/mL	20	782	257	32.89	24.37 - 44.39
	AUC_{last}, ng.h/mL	20	3312	513	15.49	10.86 - 22.09
	AUC_{∞}, ng.h/mL	11	3931	631	16.04	9.50 - 27.07
Fexofenadine (P-gp)	C_{max}, ng/mL	21	76.4	70.9	92.71	79.57 - 108.01
	AUC_{last}, ng.h/mL	21	567	398	70.10	61.06 - 80.47
	AUC_{∞}, ng.h/mL	19	639	435	68.08	58.58 - 79.12
Pioglitazone (CYP2C8)	C_{max}, ng/mL	20	435	394	90.51	79.67 - 102.82
	AUC_{last}, ng.h/mL	20	4641	3827	82.45	74.94 - 90.72
	AUC_{∞}, ng.h/mL	20	4703	3862	82.11	74.71 - 90.24
Rosuvastatin (BCRP)	C_{max}, ng/mL	20	3.56	3.53	99.09	82.68 - 118.74
	AUC_{last}, ng.h/mL	20	43.6	25.6	58.85	50.12 - 69.10
	AUC_{∞}, ng.h/mL	11	48.4	30.3	62.59	52.44 - 74.70

Induction of CYP3A4, CYP2C19 and CYP2C9, P-gp and BCRP by apalutamide suggests that UDP-glucuronosyl transferase (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR), although it should be noted that induction of CYP2C9, P-gp, BCRP was weak.

An additional clinical study was conducted to evaluate the potential drug-drug interaction between apalutamide and abiraterone-prednisone to determine the safety of the combination, and to evaluate in a descriptive manner the efficacy in subjects with mCRPC (Study 1010). The goal of this study was to provide dosing recommendations for abiraterone-prednisone in another Phase 3 study when combined with apalutamide (Study 3001) and results are included herein to support drug interaction with prednisone and further support characterization of steady-state PK with capsules and tablets. In this study, the Cmax and AUC from time 0 to 12 hours (AUC0-12) of prednisone decreased by 51% and 61%, respectively, and for prednisolone decreased by 26% and 42%, respectively, following coadministration with apalutamide in combination with abiraterone acetate. Apalutamide did not cause clinically meaningful changes in exposure to abiraterone, the Cmax and AUC from time 0 to 24 hours (AUC0-24) of abiraterone decreased by 23% and 14%, respectively.

Exposure relevant for safety evaluation

In SPARTAN (Study 003), apalutamide and N-desmethyl apalutamide exposures, measured as the AUC0-24, were 115 µg.h/mL (range: 19.8-291 µg.h/mL) and 152 µg.h/mL (range: 44.1-299 µg.h/mL), respectively.

Methods

Bioanalytical Methods

Several plasma assays for apalutamide drug with and without a combination of metabolites were used to determine concentrations in samples from clinical studies.

In general, the pre-study validations of the analytical methods are satisfactory.

These analytical methods have been described below.

Measurement of Parent Drug and Metabolites (N-desmethyl apalutamide and JNJ-56142021) in Plasma

Five assays for unchanged apalutamide and metabolites were validated at various stages of the compound development.

Analytical method [redacted]36

The above assay was adapted to include the measure metabolite N-desmethyl apalutamide. This adapted method consisted of the same sample preparation, chromatography, and mass spectrometry conditions. Besides the addition of the metabolite, another major difference was the increase of the upper limit of quantification for apalutamide from 20 to 25 µg/mL.

These 2 methods were used within a single clinical study (Study 001). At the request of the sponsor, a cross validation of the method was conducted by analyzing a set of QC samples provided by another analytical lab at three unknown concentration levels (n=6). The provided QCs were analyzed against freshly prepared calibration standards and QCs. Cross validation QC comparison demonstrated acceptable results for externally prepared ARN-509 and ARN000308 QC samples.

Analytical method [redacted]27

In 2013,, an assay was validated for the quantification of apalutamide, N-desmethyl apalutamide, and JNJ-56142021 (ARN000066 or M4). This method was only used in support of the human mass balance study, Study 006.

Analytical method [redacted]09

A new assay was developed for the determination of apalutamide and N-desmethyl apalutamide in human plasma in 2014. This method was optimized from the previous method [redacted]27 (optimization of processing and chromatography, removal of JNJ-56142021 quantitation) for support of the majority of clinical studies, including the SPARTAN study.

Analytical method

In 2 single-dose studies that involved a 60-mg dose (Studies 1015 and 1017), the concentrations of apalutamide in the later portion of the concentration-time profiles were lower than the LLOQ (0.025 µg/mL) of method [redacted]09. To improve characterization of the terminal half-life for those studies, the quantification limit of the assay was lowered to 0.005 µg/mL for both analytes.

In the studies 1015 and 1017 in which the 2 methods ([redacted]09 and [redacted]59) were used, a cross-validation for apalutamide and N-desmethyl apalutamide with study samples was performed to demonstrate that both methods have equal performance (see below).

Study 1015

A cross validation between [redacted]32 and [redacted]11 was done on a selection of 29 samples for JNJ-56021927 and 30 samples for JNJ-56142060, which already were analyzed applying [redacted]32.

The cross-validation for apalutamide complied with the acceptance criteria as 29 samples out of 29 samples (100.0%) and for N-desmethyl apalutamide as 28 samples out of 30 samples (93.3%) were within the acceptance criteria (±20%).

Study 1017

A cross validation between [redacted]32 and [redacted]11 was done on a selection of 30 samples for JNJ-56021927 and 30 samples for JNJ-56142060, which already were analyzed applying [redacted]32.

The cross-validation for apalutamide complied with the acceptance criteria as 30 samples out of 30 samples (100.0%) and for N-desmethyl apalutamide as 29 samples out of 30 samples (96.7%) were within the acceptance criteria (±20%)

Sponsor Reference No.: BA10849

The objective of the study was to cross-validate the JNJ-56021927 and JNJ-56142060 assay in human EDTA plasma between laboratories

Since the determination of apalutamide and N-desmethyl apalutamide were performed at three different analytical sites a cross-validation between all the three analytical sites were performed using QC samples (CVQC).

Cross-Validation

CVQC samples were prepared in human EDTA plasma at three levels (Low, Medium and High) and were divided in 18 separate polypropylene tubes, containing at least 1 mL of quality control sample each. After preparation, the CVQCs were organized into three sets, each consisting of 6 aliquots of CVQC low, 6 aliquots of CVQC medium and 6 aliquots of CVQC high. These samples were analyzed in house. After confirmation that the CVQC samples were analyzed successfully, aliquots were also sent to external laboratories

The cross-validation samples were successfully analysed between three laboratories.

Other analytical methods

In the clinical studies, other analytical methods have been validated and used to determine the concentration of different analytes.

These methods were used to determine the following analytes:

4ß-hydroxycholesterol , Prednisone and Prednisolone , Itraconazole and 2-Hydroxyitraconazole, Gemfibrozil, Midazolam and 1-Hydroxymidazolam, S-Warfarin and 7-Hydroxy-S-Warfarin, Omeprazole, Omeprazole Sulfone, and 5-Hydroxyomeprazole, Abiraterone and abiraterone acetate), Fexofenadine (Validation Report P1365) Pioglitazone and Rosiglitazone, Rosuvastatin and N-Desmethylrosuvastatin.

In general, the pre-study validations of the analytical methods are satisfactory.

In-Study Validation

In-study validation was conducted for the individual studies, and validation data are submitted and included in the respective bioanalytical study summaries.

In general, the in-study validation shows acceptable calibration standards and QCs. The QCs used are representative of the calibration range for all analytes.

For all analytes, the maximum storage period between collection and analysis was no longer that the current validated storage period at -70 ºC.

In general, the analysis of study samples is acceptable and the re-analysis of the study samples was well justified and handled. Dilution samples were necessary in some samples (dilution integrity for different factor were validated).

Incurred Samples Re-assay (ISR) was evaluated by additional analyses on a selection of samples plasma for apalutamide and N-desmethyl apalutamide and the others analytes. The results demonstrated reproducibility as of the incurred sample repeats met the acceptance criteria (±20%).

Chromatograms of calibrators, QCs, and subject samples (and corresponding sample sequences) from at least 20% of the subject samples analyzed are included.

Evaluation and Qualification of Models

Several models have been used to support this application:

- *Bioequivalence Trial Simulation of Apalutamide Tablets versus Capsules Following Single and Repeat Dose Administrations*

The individual concentration-versus-time plots describe the individual subject data well. Shrinkage of residual error seems acceptable, although is high in several individual parameters for Dataset B and C. [Shrinkage of individual parameters was 2.8–10.8% for Dataset A, 0.27–49% for Dataset B, and 4.15–73.5% for Dataset C. Shrinkage of residual errors was 8.0–11.1% for all Datasets]. All structural model parameters were estimated with adequate precision based on relative standard error (RSE). Fluctuations in the lowess line near the region where intensive sampling occurred are observed in the CWRES vs. TIME and CWRES vs. PRED plots for Dataset C. According to the applicant, this phenomenon may be attributed to the disparities in sample size and sampling scheme between studies in Dataset C. The applicant provided standard Goodness of Fit for apalutamide PK from Dataset C by study to justified this fact. VPC plots show that the model seems to be suitable to describe the time course of apalutamide concentrations and its variability, although data for Dataset C seems to be quite limited. Overall, each of these plots, with some limitations for plots from Dataset C, shows good concordance between

model prediction intervals and the data. VPC was not created for the concentration vs. time profiles from the ARN-509-001 study in Dataset C because of the small number of subjects (n=3).

The applicant provided a reasonable justification for using different population PK model for the bioequivalence trials simulation between capsules and tables and for the population PK model submitted as final population PK model including data of pivotal study.

- *Apalutamide mechanistic model of absorption in function of clinically relevant specifications and Physiology Based Dissolution Method in Two-Phase SGFsp-FaSSIF for 60-mg JNJ-56021927-AAA Oral Film-Coated Immediate Release Tablets*

Population Pharmacokinetics Model

In the final model all parameters were estimated with acceptable precision with a RSE <35.2% for the fixed effects and RSE<30% for the random effects. The residual error was 22.6% for apalutamide and 14.9% for JNJ-56142060. Overall, the goodness-of-fit plots of the final model for apalutamide and JNJ-56142060 against the population model prediction and individual model prediction seems to show a normal random scatter around the identity line. However, a slight over prediction trend seems to be observed with low concentrations, especially for apalutamide. The distribution of conditional weighted residuals and normalized prediction distribution errors (NPDE), as a function of the population predictions and time, supported adequacy of the model, although the same slight trend to over prediction with low concentrations is observed in those plots. The prediction corrected VPC shows that the final model described well the time course of both apalutamide and JNJ-56142060 plasma concentrations following single and multiple dose administrations, although the variability predicted during the first weeks since the first dose at single dose is higher than the observed one. The general trend in the data can be considered well captured by the population PK model.

In Dataset C, Run003, the shrinkage of IIV on *CLt* and *F* was 19% and 8%, respectively, while the shrinkage of IIV on the other parameters ranged from 42% to 74.4%. This suggest that graphical evaluation of the parameter vs potential covariate plots should be examined with great caution using Dataset C. Therefore, the applicant conducted the graphical evaluation of the covariate-parameter relationships with Dataset A. The covariate analysis was conducted using Dataset C.

- *Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-56021927 and inhibitors/inducers of CYP2C8 and CYP3A4 in Human Subjects*

Apalutamide is mainly metabolized by CYP2C8 and CYP3A4. Considered that apalutamide is a CYP3A4 and CYP2C8 inducer, and a CYP2C8 inhibitor, this might have impact on its metabolism. Therefore, over time the contribution of the different CYPs in the clearance of apalutamide might change.

It should be noted that in the guideline on the Investigation of Drug Interaction, the PBPK models are not mentioned for induction. Qualification of PBPK model for inductions should be further investigated. Therefore, the results of this population PBPK model, where induction has been included, has be considered only as supporting data and information of this PBPK was not reflected in the SmPC .

Additionally, the following limitation in relation with this PBPK model should be taken into account:

- Comparability between simulated and observed apalutamide and active metabolite (JNJ-56142060) oral PK parameters at 120 mg and 240 mg dose q.d. (capsules) is limited to observed data of 3 subject of study ARN-509-001.
- Simulation of PK profile after single oral administration of 240 mg apalutamide is conducted with capsules in healthy male subjects. It should be noted that differences of 10% in Cmax were observed

when capsules and tables formulations were compared. Healthy status was included in the final population PK as covariate with impact on PK. Therefore, these points could have certain impact on drug drug interaction results.

Additionally, the following points were reasonably justified by the applicant:

- The selection of study ARN-509-006 and 56021927PCR1012 for comparison of observed results versus simulation PK of apalutamide after single dose as well as the selection of ARN-509-001 and 56021927PCR1020 for after multiple oral administration.
- Use of different elimination parameters for apalutamide and JNJ-56142060 in the PBPK with inhibitors/inducers of CYP2C8 and CYP3A4 and in the PBPK with OCT2, MATE and OAT3 transporter substrates.
- Several apalutamide parameters used for simulations were based on individual studies instead of parameters estimated by the Population PK. However, as prediction of the AUC and Cmax ratio after co-administration with some drug is acceptable, this issue is not further pursued.

- *A physiology based pharmacokinetic approach to assess potential transporter mediated drug-drug interactions with JNJ-56021927 (apalutamide) as perpetrator in human subjects*

It should be noted that in the guideline on the Investigation of Drug Interaction, the PBPK models are not mentioned for inhibition of transport proteins. Qualification of PBPK model for inhibition of transport proteins should be further investigated. Therefore, the results of this population PBPK model should be considered only as supporting data and information of this PBPK was not reflected in the SmPC.

Additionally, the following limitation in relation with this PBPK model should be taken into account:

- Comparability between simulated and observed apalutamide and active metabolite (JNJ-56142060) oral PK parameters at 240 mg dose q.d. (capsules) is limited to observed data of 3 subject of study ARN-509-001.
- Simulation of PK profile after single oral administration of 240 mg apalutamide is conducted with capsules in healthy male subjects. It should be noted that differences of 10% in Cmax were observed when capsules and tables formulations were compared. Healthy status was included in the final population PK as covariate with impact on PK. Therefore, these points could have certain impact on drug interaction results.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Apalutamide is an orally administered AR inhibitor that binds directly to the ligand –binding domain of the AR. Apalutamide prevents AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription, a mechanism that is distinct from the first generation anti-androgen, bicalutamide. Apalutamide (IC50=16 nM) binds AR with 7- to 10-fold greater affinity than bicalutamide (median IC50=160 nM) and competes for the same binding site in the ligand-binding pocket of the receptor.

Four metabolites of apalutamide identified in preclinical species (M1, JNJ-56142047 [M2], N-desmethyl apalutamide [JNJ-56142060 or M3], and JNJ-56142021 [M4]) were assessed for their on-target effects against the AR in a cell-based assay that monitors ligand induced DNA binding.

N-desmethyl apalutamide was the most potent AR antagonist, but was still 3-fold less potent than apalutamide. Based on potency and relative clinical exposure, N-desmethyl apalutamide was considered to contribute to the clinical activity of apalutamide and was evaluated in the clinical studies.

Primary and Secondary pharmacology

Dose Selection

The anti-tumor effect of apalutamide was demonstrated in murine tumor models of CRPC in which dose-dependent tumor growth inhibition was observed over the dose range of 1, 10, 30, and 100 mg/kg/day for 28 days. In mice, there was no difference in anti-tumor effect with increase in dose from 30 to 100 mg/kg, indicating that the maximum therapeutic response was achieved at 30 mg/kg/day. The mean apalutamide concentration at 24 hours postdose in mice at 10 and 30 mg/kg/day was 3.9 and 6.1 µg/mL, respectively. In SPARTAN (Study 003), the mean Cmin of apalutamide at the dose of 240 mg once daily in subjects with NM-CRPC was 4.24 µg/mL, which was within the range that produced maximum tumor regressions in the murine tumor models.

The AR binding was assessed using FDHT-PET/CT imaging in 12 subjects with CRPC received doses of apalutamide ranging from 30 to 300 mg per day (Study 001 substudy). A decrease in FDHT uptake from baseline was observed as a function of steady-state apalutamide exposure with the relationship described using an inhibitory Emax model as a function of Cmin. The estimated maximum decrease in FDHT uptake was about 71% (RSE=30%) and the apalutamide concentration resulting in EC50 was 1.2 µg/mL (RSE=123%). Based on apalutamide steady-state Cmin and variability (CV%=27), Monte Carlo simulation suggested that approximately 100%, 100%, 99%, and 28% of subjects are predicted to exceed EC50, EC60, EC70, and EC80, respectively, at the dose of 240 mg once daily. Hence, data support that the 240 mg once daily dose used in the Phase 3 study provided adequate inhibition of the AR signaling pathway.

The safety and tolerability of apalutamide was established at doses up to 480 mg per day (N=3) with no DLTs, which provides additional safety margin for the 240 mg once daily dose.

Apalutamide 240 mg once daily was selected as the appropriate dose for the treatment of patients with NM-CRPC. The 240 mg once daily dose was evaluated in the Phase 3 study based on the safety and tolerability observed in the first-in-human study up to 480 mg, evaluation of PSA responses across the dose range, and a 12-week PSA response rate of 89% for subjects with NM-CRPC at the 240 mg dose. Inhibition of FDHT uptake, nearly plateaued in the majority of subjects at exposure observed following administration of 240 mg. The observed clinical exposure at 240 mg was well within the concentration required for maximum tumor regression in mouse xenograft models. There was no significant exposure-to-MFS relationship when analyzed by quartiles of exposure, suggesting variability of exposure including dose interruptions and dose reductions with the 240 mg dose did not significantly impact efficacy. A higher percentage of subjects (11%) in the apalutamide arm had a dose reduction due to an AE compared with the placebo arm (3%). The relationship between exposure and the incidence of adverse drug reactions was strongest with skin rash and weight decrease. The dose reduction as currently implemented in the Phase 3 clinical study by reducing apalutamide dose to 180 mg once daily, or 120 mg once daily per study protocol, is appropriate for subjects who experience an AE. The totality of the data including the exposure-response analysis based support the clinical dose of 240 mg once daily.

Dose selection of 240 mg with potential reduction based on safety and tolerability has been properly justified for patients with NM-CRPC based on evaluation of the effect of apalutamide exposure on biomarkers, safety and efficacy data. The tactics of dose reduction were properly clarified by the applicant.

Cardiac Electrophysiology

The effect of apalutamide 240 mg once daily on the QTc interval was evaluated in 45 subjects with CRPC in a dedicated QT study. At steady state, the largest ΔQTcF was 12.4 msec and the upper bound of its associated 90% CI was 16.0 msec. Across all timepoints the ΔQTcF and upper bounds of their associated 90% CIs were below the threshold of 20 msec.

PK/PD analysis showed a concentration-dependent increase in ΔQTcF and predicted a prolongation of 13.81 msec at the mean Cmax of 5.95 µg/mL at steady state with an upper bound of 2-sided 90% CI of 17.85 msec.

Overall, no large difference (ie, greater than 20 msec) was observed between the mean ΔQT interval change from baseline in subjects with CRPC treated with apalutamide 240 mg once daily. However, it should be taken into account that upper bound of the 95% one-side CI of QTc prolongation effect is higher than 10 ms. This does not imply that the drug is pro-arrhythmic. However, further electrocardiographic follow up in late phase studies is recommended. According to ICH guideline E14 –question and answers (EMA/CHMP/ICH/310133/2008), question 9, when QT study resulted in a positive finding (the 95% one-side CI of QTc prolongation effect > 10 ms) at the therapeutic dose, with a mean prolongation <20 ms, intensive monitoring of phase 3 patients is recommended in further clinical trials. Although intensive monitoring has not been conducted in the pivoltal study, 100 patients were analyses on QT prolongation, none patient reported QTc interval >480 or QTc interval increases from baseline >30 were observed. Two patients reported ventricular tachycardia event and 13 patients reported syncope event.

Exposure-Efficacy Analysis

In SPARTAN (Study 003), apalutamide and N-desmethyl apalutamide exposures, measured as the AUC0-24, were 115 µg.h/mL (range: 19.8-291 µg.h/mL) and 152 µg.h/mL (range: 44.1-299 µg.h/mL), respectively.

The exposure levels achieved at apalutamide 240 mg once daily have been proven to be efficacious in extending the MFS in subjects with NM-CRPC. No statistically significant exposure-MFS relationship was found for apalutamide and N-desmethyl apalutamide when evaluated by quartiles of exposure.

Exposure-Safety Analysis

Including the placebo group, incidence of fatigue, fall, skin rash, weight decrease, and arthralgia, at any grade, had a positive and statistically significant relationship with apalutamide exposure. The magnitude of the association varied across the different AEs and was strongest with skin rash and weight decrease. Consequently, within the exposure range observed in apalutamide-treated subjects, ie, after excluding the treatment difference with placebo, the exposure-response relationship was only statistically significant for skin rash and weight decrease.

Although some of the predicted decreases in incidence were small, dose reduction, as currently implemented in the Phase 3 clinical study, will likely improve apalutamide tolerability in subjects who develop toxicity after apalutamide treatment starts at 240 mg/day.

2.4.4. Discussion on clinical pharmacology

No dose adjustments recommendations are accepted for patients with mild and moderate hepatic impairment based on results at singe dose. However, a Phase I, single dose, clinical PK study in healthy non-cancer subjects with normal hepatic function and non-cancer subjects with severe hepatic impairment is required (see RMP). Meanwhile further information is not available on patients with severe impairment, apalutamide is not recommended in this population (see SmPC).

In 1020 study thyroid-stimulating hormone increases exceeding the upper limit of normal were observed in 48% of subjects during study drug treatment (thyroid hormone levels usually remained within normal limits). The applicant justified this increases TSH due to induction of UGT. Enzalutamide was also an inducer of UGT. However, the impact of enzalutamide on THS hormone was not notified. Apparently, these differences may be due to the lack of TSH or related thyroid function test for enzalutamide and systemic monitoring of serum TSH for apalutamide.

The following recommendations were included in the SmPC:

Concomitant use of Erleada with medications that are primarily metabolized by CYP3A4 (e.g., darunavir, felodipine, midazolam, simvastatin), CYP2C19 (e.g., diazepam, omeprazole), or CYP2C9 (e.g., warfarin, phenytoin) can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. If given with warfarin, monitor INR during Erleada treatment.

Concomitant use of Erleada with medications that are substrates of P-gp (e.g., colchicine, dabigatran etexilate, digoxin), BCRP or OATP1B1 (e.g, lapatinib, methotrexate, rosuvastatin, repaglinide) can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with Erleada and evaluate for loss of efficacy if medication is continued.

Concomitant administration of Erleada with medications that are substrates of UGT (e.g., levothyroxine, valproic acid) can result in lower exposure to these medications. Use caution if substrates of UGT must be co-administered with Erleada and evaluate for loss of efficacy.

In vitro, apalutamide is an inhibitor and inducer of CYP2B6. However, according to the applicant's justification there was limited usage of CYP2B6 substrates (eg, efavirenz, bupropion, methadone, cyclophosphamide) in subjects with NM-CRPC according to the current database for the SPARTAN study. Efavirenz and bupropion were excluded per protocol. Methadone was permitted in SPARTAN, but there was no record of methadone usage thus far. Cyclophosphamide was commonly used in the treatment of certain malignancies including lymphomas and breast cancer, but its use for treatment of subjects with prostate cancer would be rare. Given the lack of CYP2B6 substrates that are likely to be used in the target population, further in vivo drug-drug interaction assessment with CYP2B6 probe substrates was not considered to be required. Even considering this fact, conduction of an in vivo study with a probe substrate of CYP2B6 is recommended. In any case, it was clearly reflected in the SmPC that the potential of apalutamide and N-desmethyl apalutamide as an inhibitor and inducer of CYP2B6 has not been study in vivo. A recommendation of caution with substrates of CYP2B6 (including examples) was included in the SmPC.

Apalutamide is an inhibitor of the renal transporters OCT2, MATEs, and OAT3 in vitro. The potential of apalutamide to affect substrates of these renal transporters was assessed using PBPK modeling. Simulations suggest that apalutamide does not cause clinically meaningful changes in exposure to metformin (OCT2/MATEs substrate) and benzylpenicillin (OAT3 substrate). However, it should be kept in mind that in the guideline on the Investigation of Drug Interaction, the PBPK models are not mentioned for inhibition of transport proteins.

Qualification of PBPK model for inhibition of transport proteins was not sufficiently investigated. Therefore, the results of this population PBPK model were considered only as supportive data and information on this PBPK was not reflected in the SmPC.

After an additional review of all information available on QT prolongation from all studies conducted risk of potential QT prolongation in patients with clinically significant cardiovascular disease cannot be fully ruled out. Therefore, QT prolongation study in this population would be interesting. A Post Authorisation Safety Study (PASS) could be useful to better characterize the risks of use in the subgroup of population of patients with clinically significant cardiovascular disease. A prospective and interventional cohort study would ideally be the best way to evaluate the incidence of cardiovascular events and analyse follow-up of cardiovascular functions among patients with cardiovascular diseases. However, we have some concerns regarding the feasibility of this type of study at this stage, more precisely, in relation to the availability of sufficient sample size and length of follow-up to adequately address this. Thus, a feasibility assessment report of this study will be submitted. This observational study in NM-CRPC patients on ADT with clinically significant cardiovascular conditions was included in the RMP.

With current available data on QT prolongation, information currently reflected in the SmPC is considered acceptable (see SmPC 4.4 and 4.5).

The results from the Exposure-Efficacy Analysis support that 240 mg once daily dose of apalutamide provides efficacious exposure in the majority of subjects with similar efficacy across the exposure range.

The tactics of dose reduction were properly substantiated.

2.4.5. Conclusions on clinical pharmacology

Clinical pharmacology is overall well investigated and described. Relevant information is reflected in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study

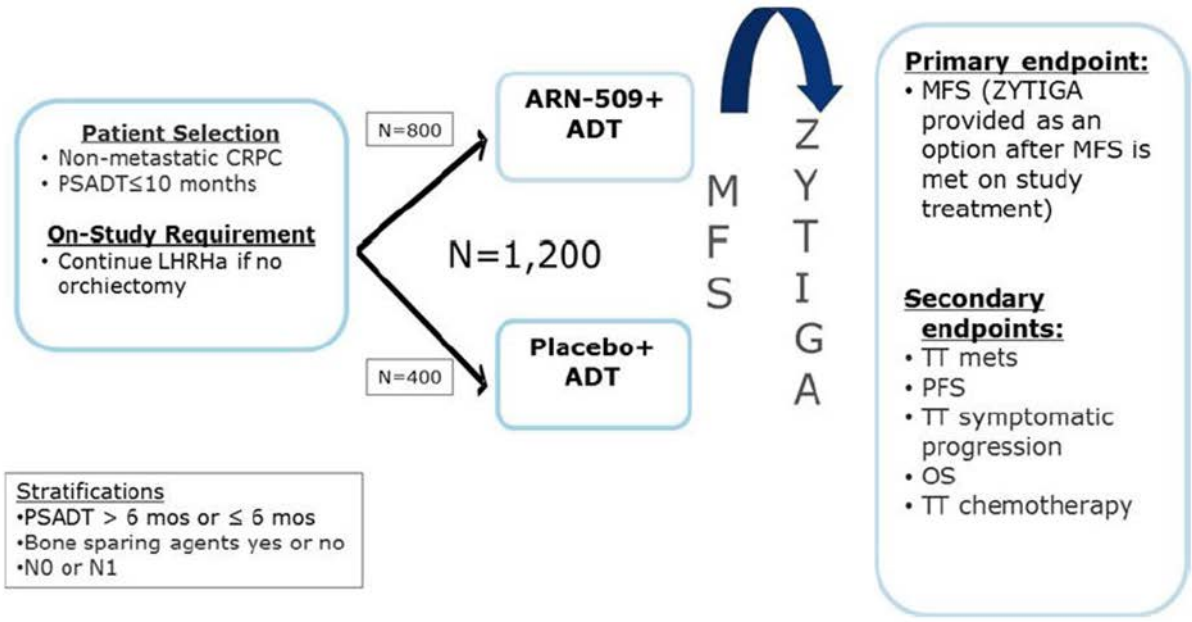
The 240 mg once daily dose was evaluated in the Phase 3 study based on the safety and tolerability observed in the first in human study at doses up to 480 mg.

2.5.2. Main study(ies)

ARN-509-003 (SPARTAN): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Apalutamide compared with placebo in subjects with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer.

Methods

Figure 5. Study design for ARN-509-003



Cross-over was not permitted.

Study Participants

Main Inclusion Criteria:

- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features with high risk for development of metastases, defined as PSADT ≤ 10 months. PSADT is calculated using at least 3 PSA values obtained during continuous ADT (androgen deprivation therapy)
- Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises, at least 1 week apart, with the last PSA > 2 ng/mL
- Surgical or medical castration with a total serum testosterone <50 ng/dL. Maintain castrate levels of testosterone within 4 weeks prior to randomization and throughout the study
- Patients currently receiving bone loss prevention treatment with bone-sparing agents must be on stable doses for at least 4 weeks prior to randomization
- Patients who received a first generation anti-androgen (e.g., bicalutamide, flutamide, nilutamide) must have at least a 4-week washout prior to randomization AND must show continuing disease (PSA) progression (an increase in PSA) after washout
- At least 4 weeks must have elapsed from the use of 5-alpha reductase inhibitors, estrogens, and any other anti-cancer therapy prior to randomization
- At least 4 weeks must have elapsed from major surgery or radiation therapy prior to randomization
- Eastern Cooperative Oncology Group Performance Status 0 or 1

- Resolution of all acute toxic effects of prior therapy or surgical procedure to Grade ≤ 1 or baseline prior to randomization
- Adequate organ function according to protocol-defined criteria
- Administration of growth factors or blood transfusions will not be allowed within 4 weeks of the hematology labs required to confirm eligibility

Main Exclusion criteria:

- Presence of confirmed distant metastases, including central nervous system and vertebral or meningeal involvement
- Symptomatic local or regional disease requiring medical intervention
- Prior treatment with second generation anti-androgens
- Prior treatment with CYP17 inhibitors
- Prior treatment with radiopharmaceutical agents, or any other investigational agent for non-metastatic castration-resistant prostate cancer
- Prior chemotherapy for prostate cancer except if administered in the adjuvant/neoadjuvant setting
- History of seizure or condition that may pre-dispose to seizure
- Concurrent therapy with protocol-defined excluded medications
- History or evidence of any of the following conditions: any prior malignancy within 5 years prior to randomization; severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events, or clinically significant ventricular arrhythmias within 6 months prior to randomization; uncontrolled hypertension; gastrointestinal disorder affecting absorption; active infection; and, any other condition that, in the opinion of the investigator, would impair the patient's ability to comply with study procedures

Treatments

Subjects were to start administration of study drug within 4 days after randomization. Apalutamide 240 mg (8 x 30 mg softgel capsules then 4 x 60 mg tablets [Amendment 6)]) or matching placebo was to be taken orally once daily with or without food. With the softgel capsules only, subjects could switch to a twice daily dosing regimen (4 tables each period) if gastrointestinal issues arose with the once daily schedule. If an apalutamide/placebo dose was missed, it was to be omitted and not made up. For the purposes of this study, a treatment cycle consisted of 4 weeks (28 days).

The dose and frequency of administration of the GnRH analogue as ADT was to follow the prescribing information in the respective label. Choice of GnRH analogue or dose could be adjusted if clinically indicated to achieve and maintain castrate concentrations of testosterone (<50 ng/dL).

Intrasubject dose interruptions and/or reductions were permitted provided that study discontinuation criteria had not been met.

Subjects received apalutamide or placebo at a dose of 240 mg given orally, daily until development of metastasis or other reason for treatment discontinuation with concurrent androgen deprivation therapy (ADT).

Objectives

Primary Objective:

- To demonstrate superiority in the metastasis-free survival (MFS) of men with high risk NM-CRPC treated with apalutamide versus placebo.

Secondary Objectives:

- To compare the following parameters in men with high risk NM-CRPC treated with apalutamide versus placebo:

- Time to metastasis (TTM)
- Progression-free survival (PFS)
- Time to symptomatic progression
- Overall survival (OS)
- Time to initiation of cytotoxic chemotherapy
- Safety and tolerability

Other objectives included assessment of prostate cancer-specific symptoms and health-related quality of life in patients treated with ARN-509 compared with placebo using FACT-P and EQ-5D, Evaluation of population pharmacokinetics of ARN-509, Evaluation of the effect of ARN-509 on ventricular repolarization in a subset of patients from selected clinical sitesand exploratory biomarkers predictive of response and resistance to ARN-509 treatment.

Outcomes/endpoints

Primary endpoint

Metastasis-free survival (MFS) was defined as the time from the date of randomization to first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis or date of death due to any cause (whichever occurs earlier) + 1 day.

Any patient without metastasis or death was censored on the date of the last RECIST 1.1 assessment. If the patient has no tumor assessment after the baseline visit they will be censored at the date of randomization +1 day.

Secondary endpoints

OS was defined as the time from the date of randomization to the date of death due to any cause +1 day (i.e., date of death or censoring– date of randomization + 1). Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

Time to metastasis (TTM), was defined as the time from randomization to first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis + 1 day. Patients without metastasis were

censored on the date of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the date of randomization + 1 day).

Progression-free survival (PFS), was to be assessed and defined as the time from randomization to first documentation of BICR-confirmed radiographic progressive disease or death due to any cause (whichever occurs first) + 1 day. Progressive disease (PD) was based on RECIST v1.1, and further defined as follows:

- For patients with at least one measurable lesion, PD was defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Furthermore, the appearance of one or more new lesions is also considered progression.
- For patients with only non-measurable disease observed on CT or MRI scans, unequivocal progression (representative of overall disease status change) or the appearance of one or more new lesions was considered progression. For new bone lesions detected on bone scans, a second imaging modality (e.g., CT or MRI) was required to confirm progression.

Progression-free survival data for patients without loco-regional disease was censored on the date of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the date of randomization + 1 day). Additional censoring rules could vary according to whether the analysis is performed for US or ex-US regulatory purposes.

Time to symptomatic progression was defined as the time from date of randomization to date of documentation in the CRF of any of the following (whichever occurs earlier) + 1 day:

- Development of a skeletal-related event (SRE): pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone.
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy.
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

Adverse event, concomitant medication, or survival follow-up CRFs might also be the source of these findings.

Time to symptomatic progression for patients who did not experience any of the events described above were censored on the date on which they were last known to be event-free.

Time to initiation of cytotoxic chemotherapy was defined as the time from randomization to documentation of a new cytotoxic chemotherapy being administered to the patient + 1 day.

Time to initiation of cytotoxic chemotherapy for patients who do not start a cytotoxic chemotherapy were censored on the date of last contact.

Other exploratory endpoints included Second Progression-free Survival (PFS2), PSA response and time to PSA progression and Health-related quality of life and cancer-specific symptoms using FACT-P and EQ-5D.

Blood and plasma samples were collected at multiple time points and archived FFPE tumor blocks or tumor slides could be analyzed for development of the F876L mutation and for high risk features (FFPE tumor blocks or tumor slides) and associations could be made with clinical endpoints as follows:

F876L mutation and other DNA mutations from cfDNA in plasma collected at Day 1 of Cycles 1, 11, 17, 25, 37, and End-of-Treatment Visit.

AR splice variants or other RNA anomalies in cfRNA in blood collected at Day 1 of Cycles 1 11, and End-of-Treatment Visit.

Global mRNA expression levels in FFPE tumor blocks or tumor slides to identify expression levels of 'high-risk' classifier genes.

Sample size

The primary efficacy analysis was event-driven and was to take place when approximately 372 MFS events had occurred. The study was designed with 90% power to detect a 30% reduction in the risk of developing metastases (HR = 0.70) for subjects receiving apalutamide, with a 2-sided α of 0.05. Based on an assumed median MFS of 25 months in the placebo arm, this treatment effect represents an increase in the median MFS of approximately 11 months (from 25 months to 36 months). Assuming an accrual period of 24 months (with 75% of the patients accrued in the second year), approximately 1,200 subjects were needed.

The study was also designed with 85% power to detect a 25% reduction (HR = 0.75) in the risk of death for subjects receiving apalutamide, based on an assumed median OS of 49 months in the placebo arm. This treatment effect represents an increase in the median OS of approximately 16 months (from 49 to 65 months).

Randomisation

Patients were randomized in a 2:1 ratio to either ARN-509 or placebo. The randomization was stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No), Loco-regional disease (N0 vs. N1).

Blinding (masking)

The study was double-blind.

Statistical methods

The primary objective of the study is to evaluate the efficacy of ARN-509 compared to placebo in patients with high risk NM-CRPC as measured by metastasis-free survival (MFS), based on blinded independent central review (BICR) of tumor assessments. If the primary efficacy endpoint of MFS is significant, the key secondary efficacy endpoints, TTM, PFS, time to symptomatic progression, OS, and time to initiation of cytotoxic chemotherapy were to be tested in that order according to the pre-specified hierarchical testing. While this is the final analysis for time to metastasis and progression free survival, it is the first interim analysis for the other endpoints and were to be tested with pre-specified O'Brian-Fleming alpha spending that provides strong control of family-wise type I error rate at 0.05 (2-sided).

Efficacy analyses will be performed on the ITT population, incorporating the randomization stratification factors as documented on the IVRS, unless otherwise specified. Time-to-event endpoints will be summarized using the Kaplan-Meier method 3 and displayed graphically where appropriate. Median event times and 2-sided 95% confidence interval for each median will be provided. Cox proportional-hazard models, including the stratification factors at baseline, will be used to estimate the hazard ratio (HR) and its 95% confidence interval (CI). Response endpoints (eg, PSA response rate) will be summarized using descriptive statistics for categorical data by treatment group. The relative risk (treatment:control) will be reported along with the associated 2-tailed

95% CIs. The two treatment groups will be compared using the stratified Mantel-Haenszel test; Fisher's exact test may be used if the expected counts in some cells are small.

Full Analysis (Intent-to-Treat) Population: All eligible patients who are randomized into the study, with study drug assignments designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized to will be included in the analyses of all efficacy and clinical benefit endpoints and patient characteristics.

Safety Analysis Population: All patients who receive at least one dose of study drug, with treatment assignments designated according to actual study treatment received will be the primary population for evaluating safety and treatment compliance and administration.

Results

Participant flow

Table 14. Treatment Disposition; Safety Population (Study ARN-509-003)

	Placebo	Apalutamide	Total
Safety Population	398	803	1201
Subjects Treated	398 (100.0%)	803 (100.0%)	1201 (100.0%)
Subjects ongoing	119 (29.9%)	489 (60.9%)	608 (50.6%)
Discontinued study treatment	279 (70.1%)	314 (39.1%)	593 (49.4%)
Reasons for Discontinuation			
Progressive disease	210 (52.8%)	155 (19.3%)	365 (30.4%)
Adverse event	25 (6.3%)	86 (10.7%)	111 (9.2%)
Withdrawal by subject	39 (9.8%)	54 (6.7%)	93 (7.7%)
	Placebo	Apalutamide	Total
Other	2 (0.5%)	9 (1.1%)	11 (0.9%)
Noncompliance with study procedures	0	6 (0.7%)	6 (0.5%)
Protocol violation	2 (0.5%)	3 (0.4%)	5 (0.4%)
Lost to follow-up	1 (0.3%)	1 (0.1%)	2 (0.2%)

Note: Percent is based on safety population of each treatment group (as denominator).

Recruitment

Two thousand one hundred thirty-two (2,132) subjects signed the informed consent and were screened. Of the 925 patients who were ineligible, 517 subjects were ineligible due to the presence of metastatic disease at screening.

From 14 October 2013 (first subject randomized) to 15 December 2016 (last subject randomized) 1207 subjects (806 subjects in the apalutamide arm and 401 subjects in the placebo arm) were randomized (ITT population) at 332 sites from 26 countries.

Conduct of the study

Protocol amendments

There were 8 amendments to the protocol. The first and second amendments to the protocol were adopted before any study-related procedures had begun. Key changes are summarized in the below table.

Table 15. Summary of Protocol Amendments for ARN-509-003

Amendment INT-1 (11 January 2013, non-substantial)	• Removed requirement for refrigerated conditions of shipping and storage of ARN-509/placebo softgel capsules.
Amendment INT-2 (08 May 2013, substantial)	• Removed ARN-509/placebo storage conditions from the protocol and presented that storage instructions are found on the packaging label • Modified the description of the frequency of tumor assessments with respect to randomization date rather than first dose of study drug. • Clarified that subjects should remain on study until they have disease progression confirmed by BICR. If the subject discontinues treatment before confirmed disease progression, the schedule of tumor assessment (every 16 weeks from randomization) should continue until disease progression. • Modified eligibility criteria (Inclusion #1, Exclusion #1, Exclusion #5, and Exclusion 6. • Clarification to definition of end of study treatment and end of study with respect to expected length of subject participation. • Additional instructions were added regarding missed doses (Section 5.3.4). • Revised requirements for collection of concomitant medication information. • Clarification regarding reporting of disease progression as an SAE, only disease progression with a fatal outcome should be reported as an SAE.
Amendment INT-3 (11 March 2014, substantial)	• Statistical analysis plan for the secondary endpoints was modified • A provision of abiraterone acetate plus prednisolone as a subsequent therapy for eligible subjects (except in Japan) was added • Additional exploratory biomarker research was added • Removed urinalysis testing from procedures • Population PK and PRO analyses were modified
Amendment INT-4 (16 June 2014, substantial)	• This amendment was never implemented but the changes described for this amendment were incorporated in Amendment INT-5.
Amendment INT-5 (1 July 2014, substantial)	• Incorporated investigator feedback for Inclusion criteria #1 and 2 in order to clarify the definitions of prostate specific antigen doubling time (PSADT) and castration-resistance so that the intended homogenous and high risk patient population is enrolled. Section 5.1 is also being revised to reflect the change to Inclusion Criterion #1. The addition of an optional prescreening period is being incorporated to allow investigators time to obtain the required number of prostate-specific antigen (PSA) values for meeting the study eligibility criteria • Added a 24-month collection time period during which PSA values used to calculate the PSADT can be obtained. This change was made shortly after finalization of the previous amendment.
Amendment INT-6 (18 May 2015, substantial)	• Study drug formulation changed from softgel capsules to tablet. Subjects who were receiving the softgel capsules were switched to tablets (commercial formulation). Subjects who were newly enrolled were administered the tablet formulation.
Amendment 7 (1 June 2016, non-substantial)	• The frequency of visits after Cycle 7 was reduced. Clarified that collection of medical resource utilization (MRU) was to continue during the Long-term Follow-up Phase.
Amendment 8 (15 March 2017, substantial)	• Hierarchical testing of secondary endpoints including a provision for re-estimating the timepoints for next analysis of symptomatic progression and other secondary endpoints was enacted • Added details for placebo subjects to receive apalutamide, in the event of a positive study result and unblinding. • Clarification for criteria for disease progression for administration of abiraterone acetate, if the study is unblinded.

Protocol deviations

Major protocol deviations identified during the study are summarized in the below table.

Table 16. Summary of Subjects with Major Protocol Deviations; Intent-to-treat Population (Study ARN- 509-003)

	Placebo	Apalutamide	Total
ITT Population	401	806	1207
Subjects with major protocol deviations	37 (9.2%)	80 (9.9%)	117 (9.7%)
Subject did not meet inclusion or exclusion criteria	16 (4.0%)	42 (5.2%)	58 (4.8%)
Subject received a disallowed concomitant treatment	9 (2.2%)	21 (2.6%)	30 (2.5%)
Subject received wrong treatment or incorrect dose	9 (2.2%)	16 (2.0%)	25 (2.1%)
Other non-compliance	4 (1.0%)	2 (0.2%)	6 (0.5%)
Incorrect study treatment	0	3 (0.4%)	3 (0.2%)
Safety assessment deviation	0	2 (0.2%)	2 (0.2%)
Subject did not withdraw as per protocol	1 (0.2%)	0	1 (0.1%)

For each deviation, subjects are included only once, even if they experienced multiple events in that deviation. Subjects may appear in more than one category.

Baseline data

Table 17. Summary of Demographics; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide	Total
ITT Population	401	806	1207
Age, years			
N	401	806	1207
Mean (SD)	74.1 (7.92)	73.7 (8.07)	73.9 (8.02)
Median	74.0	74.0	74.0
Range	(52; 97)	(48; 94)	(48; 97)
<65	43 (10.7%)	106 (13.2%)	149 (12.3%)
65-69	78 (19.5%)	137 (17.0%)	215 (17.8%)
70-74	91 (22.7%)	170 (21.1%)	261 (21.6%)
75-79	80 (20.0%)	185 (23.0%)	265 (22.0%)
80-84	71 (17.7%)	144 (17.9%)	215 (17.8%)
≥ 85	38 (9.5%)	64 (7.9%)	102 (8.5%)
Race			
N	401	806	1207
American Indian or Alaska Native	0	4 (0.5%)	4 (0.3%)
Asian	47 (11.7%)	93 (11.5%)	140 (11.6%)
Black or African American	20 (5.0%)	48 (6.0%)	68 (5.6%)
Native Hawaiian or other Pacific Islander	0	0	0
White	276 (68.8%)	524 (65.0%)	800 (66.3%)
Other	1 (0.2%)	1 (0.1%)	2 (0.2%)
Multiple	0	1 (0.1%)	1 (0.1%)
Not reported	57 (14.2%)	135 (16.7%)	192 (15.9%)
Ethnicity			
N	401	806	1207
Hispanic or Latino	5 (1.2%)	11 (1.4%)	16 (1.3%)
Not Hispanic or Latino	338 (84.3%)	659 (81.8%)	997 (82.6%)
Not reported	58 (14.5%)	136 (16.9%)	194 (16.1%)
Weight, kg			
N	399	801	1200
Mean (SD)	85.4 (17.41)	87.8 (19.45)	87.0 (18.82)
Median	83.2	85.0	84.4
Range	(43; 161)	(45; 182)	(43; 182)
Height, cm			
N	390	789	1179
Mean (SD)	172.7 (7.98)	172.9 (7.93)	172.8 (7.95)
Median	172.0	173.0	173.0
Range	(149; 194)	(140; 196)	(140; 196)

Table 18. Summary of Prostate Cancer Clinical Disease Characteristics at Diagnosis and Baseline; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide	Total
ITT Population	401	806	1207
Time from initial diagnosis to randomization (years)			
N	400	806	1206
Mean (SD)	8.78 (5.099)	8.93 (5.227)	8.88 (5.183)
Median	7.85	7.95	7.90
Range	(0.8; 26.3)	(0.3; 30.4)	(0.3; 30.4)
Tumor stage at diagnosis			
N	394	794	1188
T1	63 (16.0%)	141 (17.8%)	204 (17.2%)
T2	123 (31.2%)	265 (33.4%)	388 (32.7%)
T3	163 (41.4%)	296 (37.3%)	459 (38.6%)
T4	16 (4.1%)	32 (4.0%)	48 (4.0%)
TX	29 (7.4%)	60 (7.6%)	89 (7.5%)
Lymph node stage at diagnosis			
N	395	799	1194
N0	273 (69.1%)	550 (68.8%)	823 (68.9%)
N1	61 (15.4%)	118 (14.8%)	179 (15.0%)
NX	61 (15.4%)	131 (16.4%)	192 (16.1%)
Metastasis stage at diagnosis			
N	400	806	1206
M0	400 (100.0%)	806 (100.0%)	1206 (100.0%)
Gleason score at initial diagnosis			
N	387	784	1171
<7	72 (18.6%)	152 (19.4%)	224 (19.1%)
7	146 (37.7%)	291 (37.1%)	437 (37.3%)
3+4	65 (16.8%)	157 (20.0%)	222 (19.0%)
4+3	77 (19.9%)	125 (15.9%)	202 (17.3%)
>7	169 (43.7%)	341 (43.5%)	510 (43.6%)
IVRS PSA Doubling Time (months)			
N	401	806	1207
Mean (SD)	4.76 (2.247)	4.74 (2.305)	4.75 (2.285)
Median	4.50	4.40	4.40
Range	(0.7; 10.0)	(0.8; 10.0)	(0.7; 10.0)
ECOG Performance Status Score			
N	400	806	1206
0	311 (77.8%)	623 (77.3%)	934 (77.4%)
1	89 (22.3%)	183 (22.7%)	272 (22.6%)

ECOG=Eastern Cooperative Oncology Arm; NX=unknown; PSA=Prostate-specific Antigen

Table 19. Summary of Baseline Laboratory Parameters; Intent-to-treat Population (Study ARN-509- 003)

	Placebo	Apalutamide	Total
ITT Population	401	806	1207
PSA (ng/mL)			
N	401	806	1207
Mean (SD)	15.93 (23.749)	14.90 (22.533)	15.24 (22.939)
Median	7.96	7.78	7.80
Range	(1.1; 291.8)	(0.1; 294.8)	(0.1; 294.8)
Hemoglobin (g/L)			
N	401	806	1207
Mean (SD)	132.91 (13.028)	132.46 (12.398)	132.61 (12.607)
Median	134.00	133.00	133.00
Range	(92.0; 202.0)	(94.0; 221.0)	(92.0; 221.0)
Lactate Dehydrogenase (%)			
N	78	147	225
Mean (SD)	181.17 (31.140)	196.04 (44.291)	190.88 (40.771)
Median	176.50	186.00	182.00
Range	(131.0; 293.0)	(132.0; 370.0)	(131.0; 370.0)
Alkaline Phosphatase (U/L)			
N	401	806	1207
Mean (SD)	80.21 (23.781)	80.53 (25.632)	80.43 (25.023)
Median	78.00	77.00	78.00
Range	(29.0; 257.0)	(3.0; 353.0)	(3.0; 353.0)
Testosterone (nmol/L)			
N	401	806	1207
Mean (SD)	0.87 (0.462)	0.86 (0.435)	0.86 (0.444)
Median	0.80	0.80	0.80
Range	(0.3; 2.8)	(0.3; 3.1)	(0.3; 3.1)

Table 20. Overall Summary of Prior Prostate Cancer Therapy; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide	Total
ITT population	401	806	1207
Previous prostate cancer therapy			
N	401	803	1204
Surgery or radiotherapy	307 (76.6%)	617 (76.6%)	924 (76.6%)
Surgery only	69 (17.2%)	159 (19.7%)	228 (18.9%)
Radiotherapy only	85 (21.2%)	157 (19.5%)	242 (20.0%)
Both surgery and radiotherapy	153 (38.2%)	301 (37.3%)	454 (37.6%)
Hormonal therapy	400 (99.8%)	801 (99.4%)	1201 (99.5%)
GnRHa	387 (96.5%)	780 (96.8%)	1167 (96.7%)
First generation antiandrogen	290 (72.3%)	592 (73.4%)	882 (73.1%)
Orchiectomy	24 (6.0%)	47 (5.8%)	71 (5.9%)
Other	9 (2.2%)	17 (2.1%)	26 (2.2%)
Chemotherapy	7 (1.7%)	17 (2.1%)	24 (2.0%)
Other	32 (8.0%)	64 (7.9%)	96 (8.0%)

GnRHa=gonadotropin releasing hormone analog
Chemotherapy: either adjuvant or neoadjuvant

Common concomitant medications, reported for ≥50% of subjects included analgesics (apalutamide: 61%; placebo: 57%), agents acting on the renin-angiotensin system (apalutamide: 55%; placebo: 50%), and lipid modifying agents (apalutamide: 50%; placebo: 51%).

Numbers analysed

Efficacy analyses were performed using the ITT population, which included 1207 randomized subjects (806 subjects in the apalutamide arm and 401 subjects in the placebo arm). As of the clinical cut-off date (19 May 2017), the median survival follow-up time for all subjects was 20.3 months.

Outcomes and estimation

Primary Efficacy Analysis- Metastasis-Free Survival by Blinded Independent Central Review

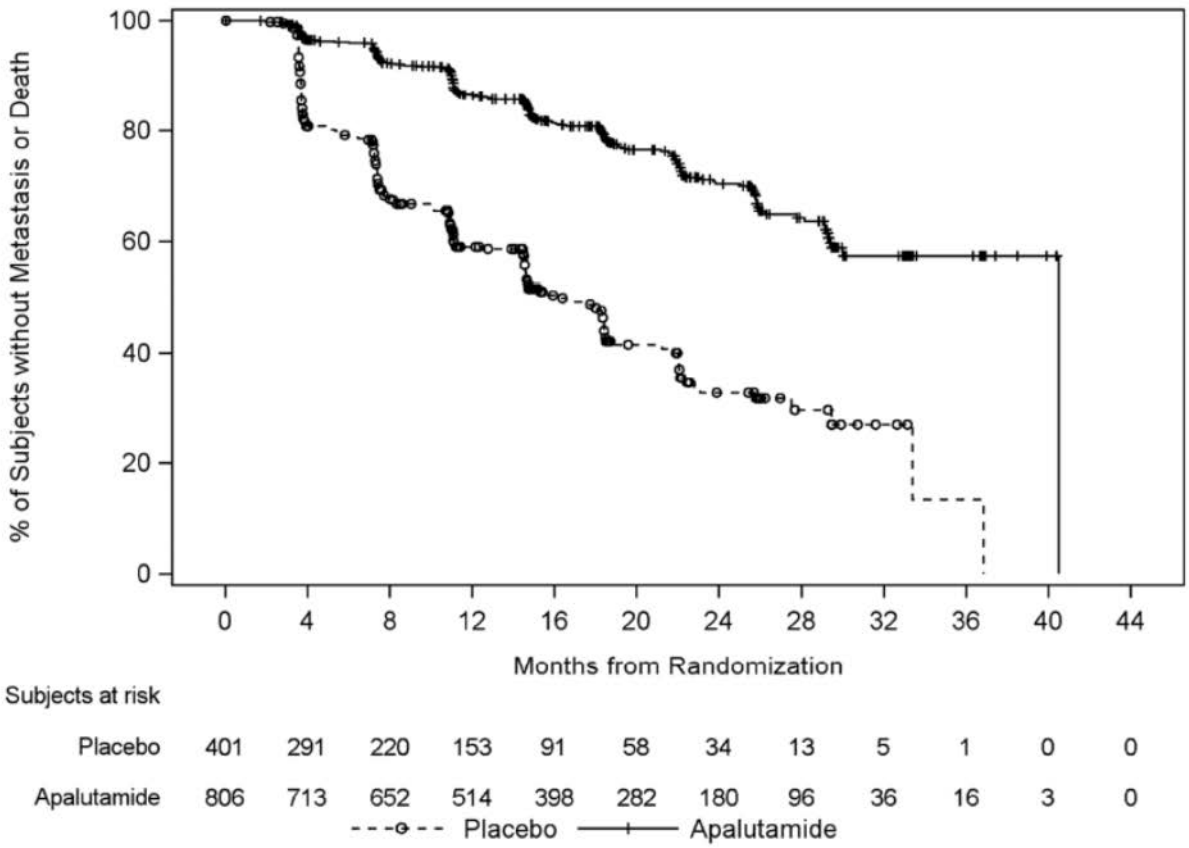
One hundred eighty-four (23%) subjects in the apalutamide arm and 194 (48%) subjects in the placebo arm were reported with distant metastases by BICR or had died (Table 21) (based on ex-US censoring rules is presented in Table 33).

Table 21. Summary of Blinded Independent Central Review (BICR) Metastasis-Free Survival (MFS) for US Regulatory – Stratified Analysis; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Event	194 (48.4%)	184 (22.8%)
Censored	207 (51.6%)	622 (77.2%)
MFS (months)		
25th percentile (95% CI)	7.26 (5.55, 7.43)	21.88 (18.50, 23.72)
Median (95% CI)	16.20 (14.59, 18.40)	40.51 (NE, NE)
75th percentile (95% CI)	33.38 (25.76, 36.83)	40.51 (NE, NE)
Range	(0.0+, 36.8)	(0.0+, 40.5)
12-month event-free rate (95% CI)	0.591 (0.536, 0.641)	0.865 (0.838, 0.889)
24-month event-free rate (95% CI)	0.326 (0.260, 0.394)	0.704 (0.660, 0.744)
36-month event-free rate (95% CI)	0.134 (0.017, 0.371)	0.574 (0.506, 0.637)
p-value[a]		<.0001
Hazard ratio (95% CI) [b]		0.280 (0.227,0.346)

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment arm, stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio < 1 favors active treatment.
Note: +=censored observation, NE=not estimable

Figure 6. Kaplan-Meier Plot of Blinded Independent Central Review (BICR) Metastasis-Free Survival (MFS) for US Regulatory; Intent-to-treat Population (Study ARN-509-003)



Results of the analysis of MFS with radiographic assessment by the investigator are consistent with MFS results by BICR. Treatment with apalutamide significantly decreased the risk of metastasis or death by 75% compared with placebo (HR=0.251; 95% CI: 0.205, 0.308; p<0.0001). The median TTM or death was 41.2 months for the apalutamide arm and 14.6 months for the placebo arm. At 12 months, 86% of subjects in the apalutamide arm and 54% of subjects in the placebo arm were event-free; at 24 months, the event-free rate was 72% compared with 28%, respectively.

Sensitivity Analysis of Metastasis-Free Survival

In the conduct of this study, it was noted that 152 (13%) subjects were incorrectly stratified at the time of randomization. As a sensitivity analysis of the MFS results, a stratified analysis of MFS was performed using corrected stratification factors. The results of this analysis (HR=0.286; 95% CI: 0.233, 0.352; p<0.0001) were consistent with those of the stratified analysis.

An MFS sensitivity analysis was performed using corrected stratification factors and ex-US censoring rules. The results of this analysis (HR=0.303; 95% CI: 0.249, 0.370; p<0.0001) were consistent with those of the stratified analysis.

The non-stratified analysis of MFS by BICR using US censoring rules and ex-US censoring rules were provided. The results of these analyses (HR=0.295; 95% CI: 0.240, 0.362; p<0.0001 and HR=0.310; 95% CI: 0.256, 0.377; p<0.0001, respectively) were consistent with the stratified analysis.

Secondary Endpoint Analyses- Time to Metastasis

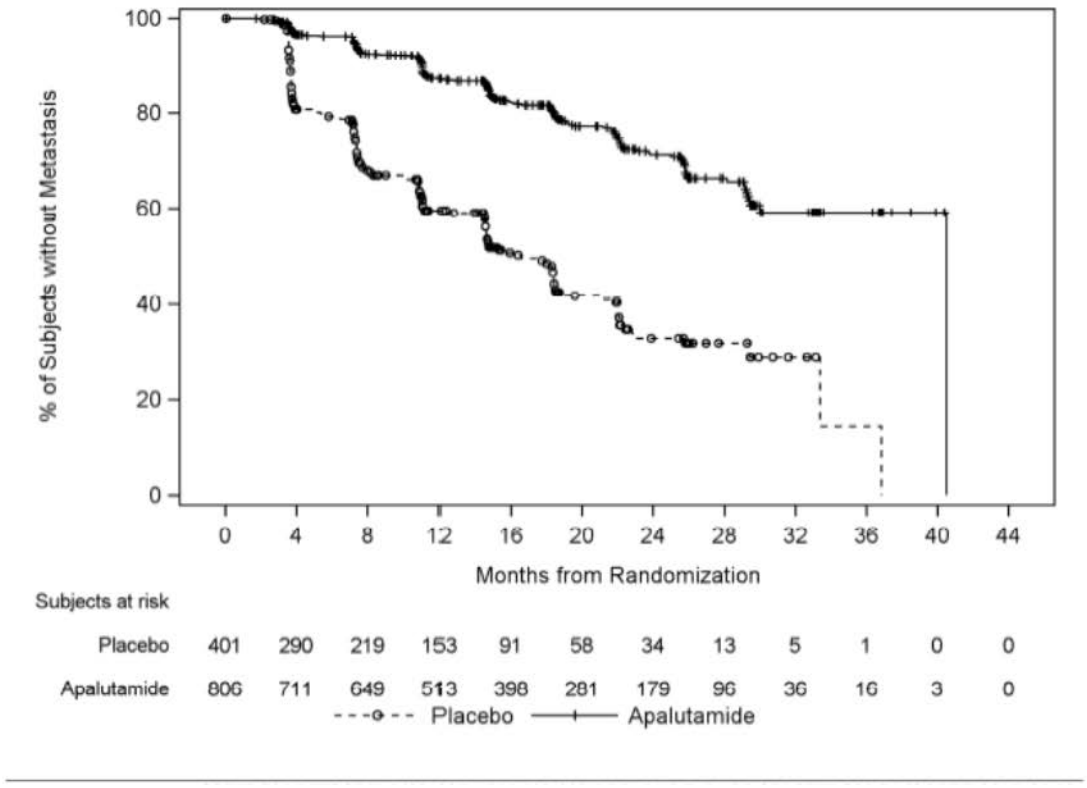
Time to metastasis (TTM) is defined as the time from randomization to BICR-confirmed radiographically detected bone or soft tissue distant metastasis. This was prespecified as the final analysis for TTM. Metastasis-free survival was statistically significant, hence, according to the pre specified hierarchical testing procedure, TTM is considered to be statistically significant if the p-value is less than 0.05. (Table 22). (data based on ex-US censoring rules is presented in Table 33.)

Table 22. Summary of Blinded Independent Central Review (BICR) Time to Metastasis for US Regulatory – Stratified Analysis; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Event	191 (47.6%)	175 (21.7%)
Censored	210 (52.4%)	631 (78.3%)
Time to Metastasis (months)		
25th percentile (95% CI)	7.29 (5.55, 7.46)	21.95 (18.89, 25.03)
Median (95% CI)	16.59 (14.59, 18.46)	40.51 (NE, NE)
75th percentile (95% CI)	33.38 (29.47, 36.83)	40.51 (NE, NE)
Range	(0.0+, 36.8)	(0.0+, 40.5)
12-month event-free rate (95% CI)	0.595 (0.540, 0.645)	0.873 (0.846, 0.896)
24-month event-free rate (95% CI)	0.329 (0.262, 0.397)	0.711 (0.667, 0.751)
36-month event-free rate (95% CI)	0.145 (0.018, 0.395)	0.591 (0.523, 0.654)
p-value[a]		<.0001
Hazard ratio (95% CI) [b]		0.271 (0.219,0.335)

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 7. Kaplan-Meier Plots of Blinded Independent Central Review (BICR) Time to Metastasis for US Regulatory; Intent-to-treat Population (Study ARN-509-003)



Secondary Endpoint Analyses- Progression-free Survival

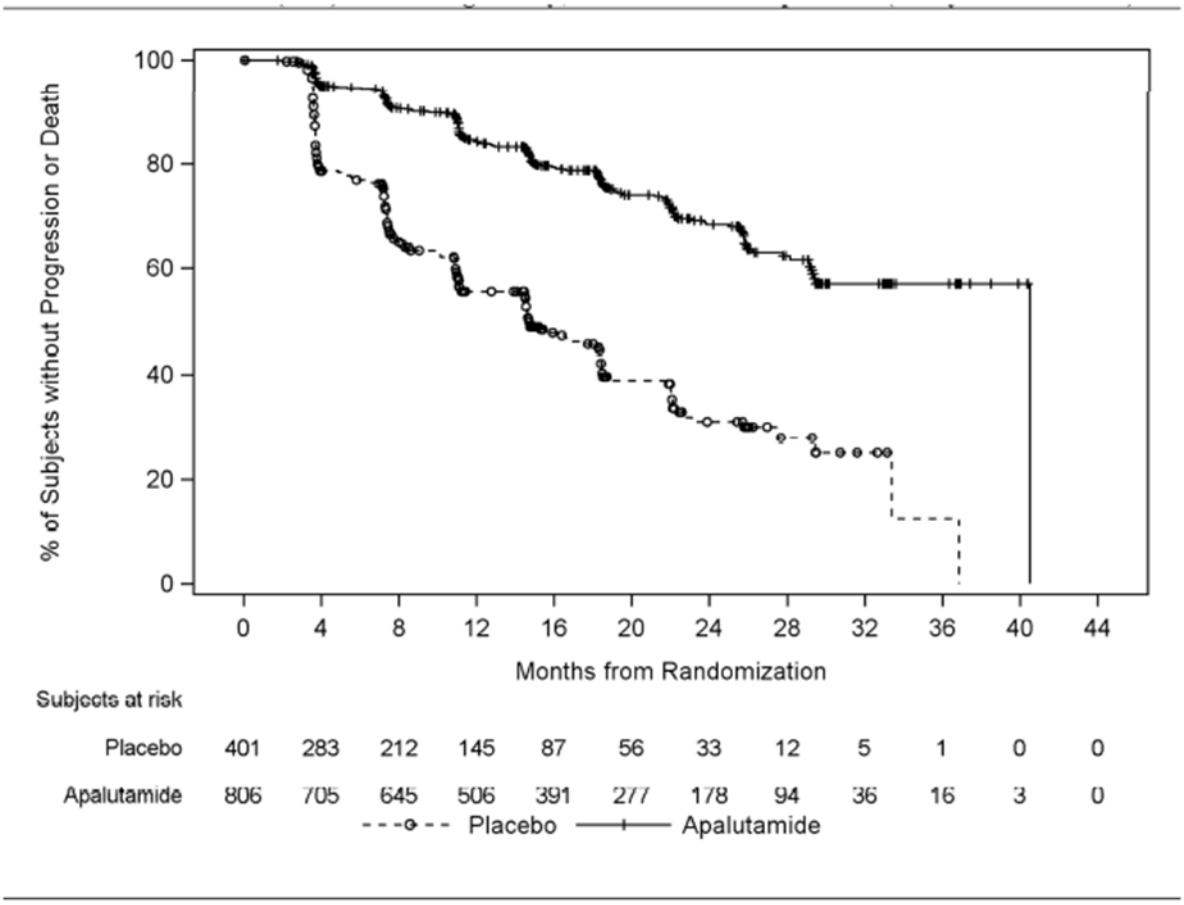
Progression-free survival is defined as the time from randomization to first BICR-confirmed radiographic progressive disease (distant or local/regional) or death due to any cause. This was prespecified as the final analysis for PFS. Time to metastasis was statistically significant, hence, according to the pre-specified hierarchical testing procedure, PFS is considered to be statistically significant if the p-value is less than 0.05. (Table 23). (data based on ex-US censoring rules is presented in Table 33.)

Table 23. Summary of Blinded Independent Central Review (BICR) Progression-Free Survival (PFS) for US Regulatory – Stratified Analysis; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Event	204 (50.9%)	200 (24.8%)
Censored	197 (49.1%)	606 (75.2%)
PFS (months)		
25th percentile (95% CI)	7.23 (3.88, 7.36)	19.09 (18.20, 22.11)
Median (95% CI)	14.72 (14.49, 18.37)	40.51 (NE, NE)
75th percentile (95% CI)	33.38 (23.06, 36.83)	40.51 (NE, NE)
Range	(0.0+, 36.8)	(0.0+, 40.5)
12-month event-free rate (95% CI)	0.555 (0.501, 0.606)	0.844 (0.815, 0.869)
24-month event-free rate (95% CI)	0.310 (0.245, 0.376)	0.684 (0.640, 0.724)
36-month event-free rate (95% CI)	0.125 (0.016, 0.351)	0.571 (0.508, 0.628)
p-value[a]		<.0001
Hazard ratio (95% CI) [b]		0.291 (0.238,0.356)

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 8. Kaplan-Meier Plot of Blinded Independent Central Review (BICR) Progression-Free Survival (PFS) for US Regulatory; Intent-to-treat Population (Study ARN-509-003)



Secondary Endpoint Analyses- Time to Symptomatic Progression

Time to symptomatic progression is defined as the time from randomization to development of a skeletal-related event, pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy, or development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy. This was prespecified in the hierarchical testing scheme to be tested for significance if MFS, TTM, and PFS were all significant. The alpha level for this test at this interim is 0.00008 using the O'Brien-Fleming type alpha spending function to control the overall alpha at 0.05 for this endpoint with this interim analysis.

Table 24. Summary of Time to Symptomatic Progression – Stratified Analysis; Intent-to treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Event	63 (15.7%)	64 (7.9%)
Censored	338 (84.3%)	742 (92.1%)
Time to Symptomatic Progression (months)		
25th percentile (95% CI)	29.70 (21.91, 36.83)	NE (32.07, NE)
Median (95% CI)	NE (36.83, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 39.5+)	(0.0+, 40.6+)
12-month event-free rate (95% CI)	0.922 (0.889, 0.946)	0.970 (0.955, 0.980)
24-month event-free rate (95% CI)	0.795 (0.738, 0.842)	0.895 (0.863, 0.920)
36-month event-free rate (95% CI)	0.644 (0.506, 0.752)	0.777 (0.660, 0.858)
p-value[a]		<.0001
Hazard ratio (95% CI) [b]		0.447 (0.315,0.634)

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 9. Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population (Study ARN-509-003)

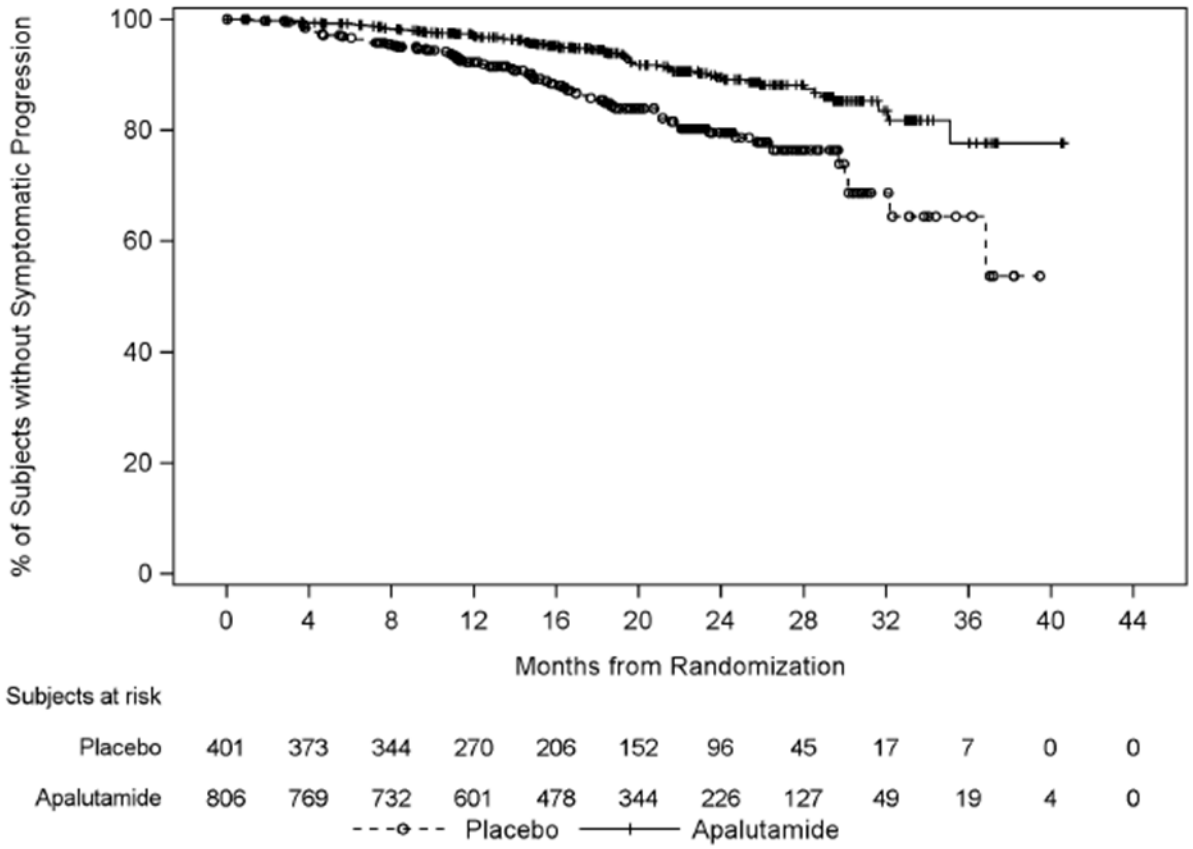


Table 25. Summary of the Type of Symptomatic Progression; Subjects with Symptomatic Progression (Study ARN-509-003)

	Placebo	Apalutamide
Subjects who had symptomatic progression	63	64
Pain progression or worsening of disease-related symptoms only	23 (36.5%)	24 (37.5%)
Skeletal-related event only	12 (19.0%)	15 (23.4%)
Loco-regional tumor progression only	17 (27.0%)	12 (18.8%)
Skeletal-related event, pain progression or worsening of disease-related symptoms	1 (1.6%)	5 (7.8%)
Unknown	4 (6.3%)	4 (6.3%)
Pain progression or worsening of disease-related symptoms, loco-regional tumor progression	2 (3.2%)	2 (3.1%)
Skeletal-related event, loco-regional tumor progression	4 (6.3%)	1 (1.6%)
Skeletal-related event, pain progression or worsening of disease-related symptoms, loco-regional tumor progression	0	1 (1.6%)

Secondary Endpoint Analyses- Overall Survival

This is the first of 2 interim analyses of OS as prespecified in the protocol. Overall survival was to be tested if MFS, TTM, PFS, and time to symptomatic progression were all statistically significant.

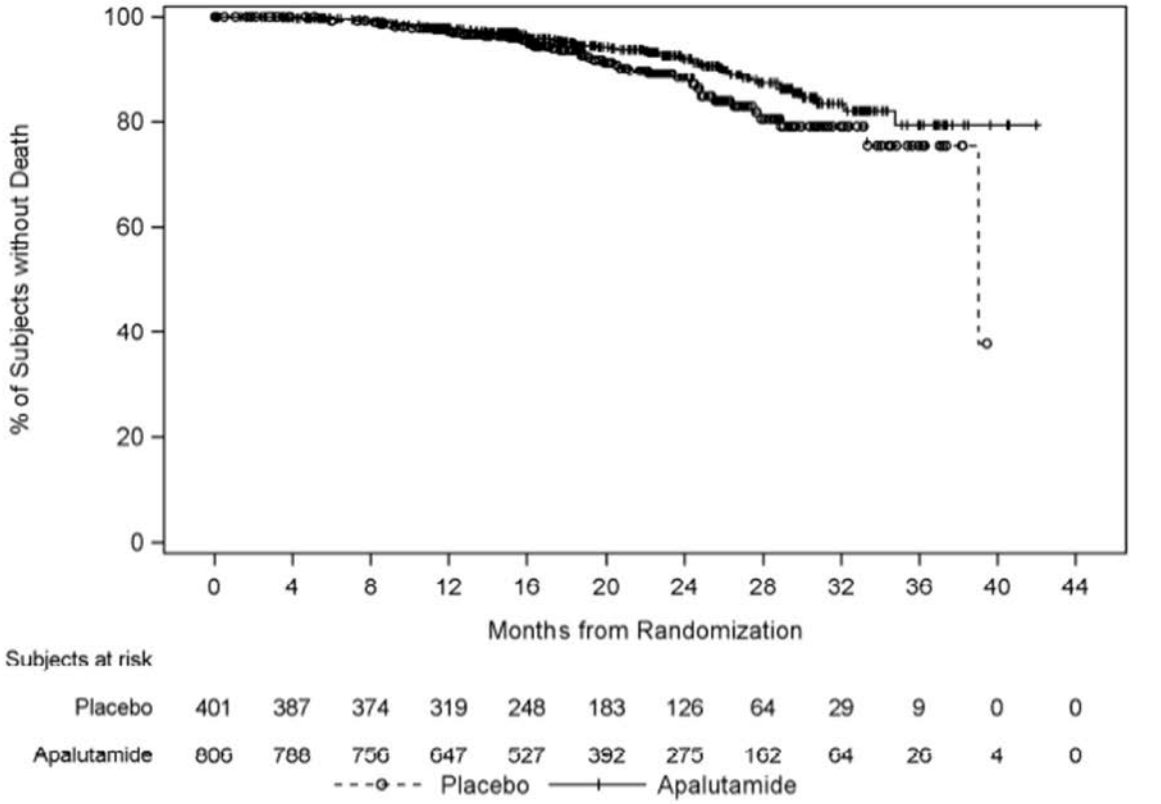
The analysis did not reach the prespecified statistical significance level based on the O'Brien-Fleming efficacy boundary (p=0.000012). The median survival was not reached in the apalutamide arm and was 39.0 months in the placebo arm.

Table 26. Summary of Overall Survival (OS) – Stratified Analysis; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Event	42 (10.5%)	62 (7.7%)
Censored	359 (89.5%)	744 (92.3%)
OS (months)		
25th percentile (95% CI)	39.03 (27.50, NE)	NE (34.76, NE)
Median (95% CI)	39.03 (39.03, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (39.03, NE)	NE (NE, NE)
Range	(0.0+, 39.5+)	(0.0+, 42.0+)
1-year survival rate (95% CI)	0.973 (0.950, 0.985)	0.979 (0.966, 0.987)
2-year survival rate (95% CI)	0.884 (0.835, 0.919)	0.920 (0.892, 0.941)
3-year survival rate (95% CI)	0.755 (0.645, 0.835)	0.794 (0.709, 0.857)
p-value[a]		0.0742
Hazard ratio (95% CI) [b]		0.700 (0.472,1.038)

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 10. Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study ARN-509 003)



A non-stratified analysis of OS showed results consistent with the stratified analysis (HR=0.684; 95% CI: 0.462,1.012; p=0.0557.

Secondary Endpoint Analyses- Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy is defined as the time from randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. This is the first interim analysis for time to initiation of cytotoxic chemotherapy. A formal statistical assessment of this endpoint was to be performed if MFS, TTM, PFS, time to symptomatic progression, and OS were all statistically significant.

Figure 11. Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy; Intent-to-treat Population (Study ARN-509-003)

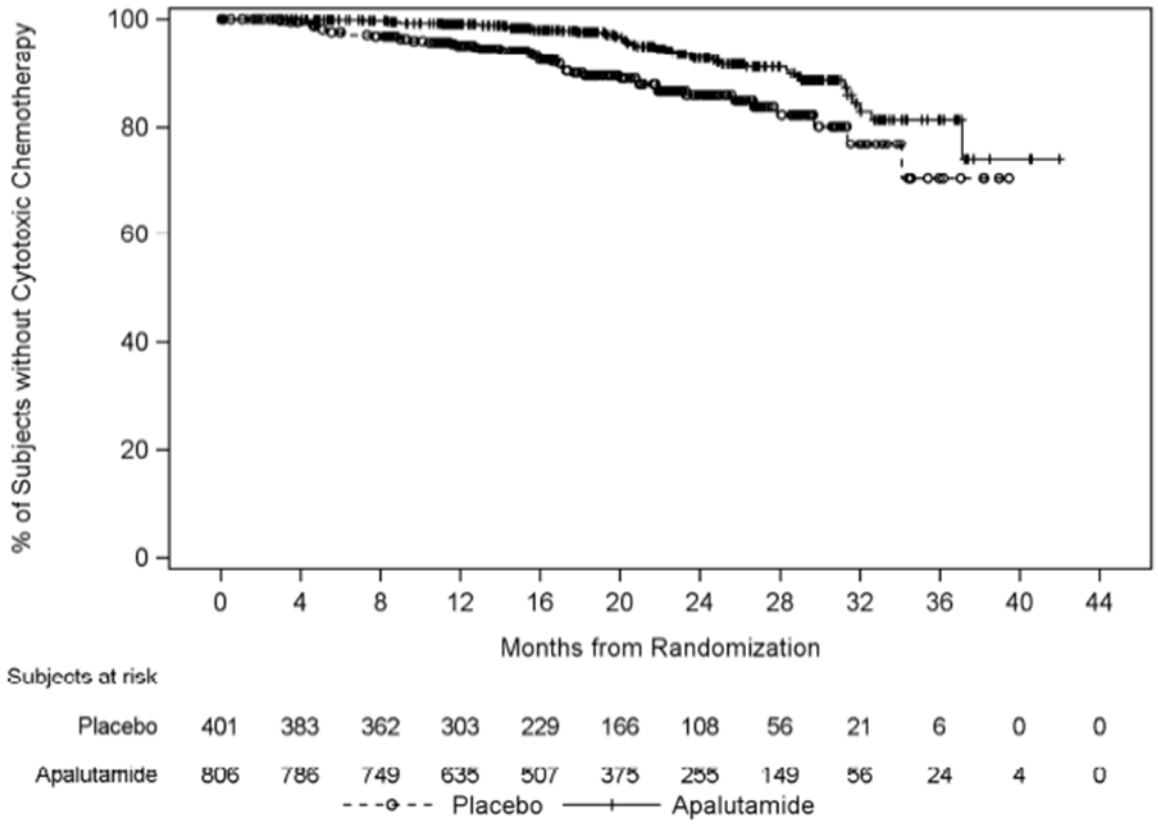


Table 27. Summary of Time to Initiation of Cytotoxic Chemotherapy – Stratified Analysis; Intent-to-treat Population (Study ARN-509-003)

ITT Population	Placebo 401	Apalutamide 806
Event	63 (15.7%)	75 (9.3%)
Censored	338 (84.3%)	731 (90.7%)
Time to Initiation of Cytotoxic Chemotherapy (months)		
25th percentile (95% CI)	43.27 (34.10, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 51.8+)	(0.0+, 51.6+)
12-month event-free rate (95% CI)	0.950 (0.922, 0.968)	0.991 (0.981, 0.996)
24-month event-free rate (95% CI)	0.863 (0.822, 0.895)	0.942 (0.922, 0.957)
36-month event-free rate (95% CI)	0.802 (0.749, 0.845)	0.874 (0.841, 0.901)

Note: + = censored observation, NE = not estimable

(data based on ex-US censoring rules is presented in Table 33.)

Other Efficacy Endpoints- Patient-Reported Outcomes

Patient-reported outcome results indicated that there was no detriment to overall health-related quality of life with the addition of apalutamide to ADT. Similar mean changes from baseline or median time to worsening in the FACT-P were observed in the 2 treatment arms. For nearly all time points, no differences between apalutamide and placebo were observed in change from baseline across the EQ-5D index or VAS.

However, the Applicant failed to provide the information of improvement of HRQoL in patient in the apalutamide arm. For use of apalutamide in these clinical settings for nonmetastatic cancer, it seems to be important supporting finding that should be analysed and improvement clearly showed. After requesting, the Applicant provided an additional information on differences in HRQoL for patients in apalutamide versus placebo arms. Although the Applicant claims that “There was little to no change observed around the median onset of hypertension, rash, and fatigue compared with baseline across the FACT-P total score and subscales. For all selected TEAEs, the HRQoL scores were similar throughout the TEAE period compared with baseline regardless of treatment arm”, the absence of proper statistical analysis providing differences between arms using appropriate tests gives no information for making such a conclusion. For example, in the Table E8 provided by the Applicant, it can be clearly seen that more selected adverse events (AEs) occur in the apalutamide arm in comparison with placebo. The Applicant did not performed analysis of statistical significance providing tables of per cent of distribution of AEs between groups. That makes the proper conclusion on statistical difference impossible. However, even looking on raw data, the higher prevalence of AEs in apalutamide arm can be mentioned.

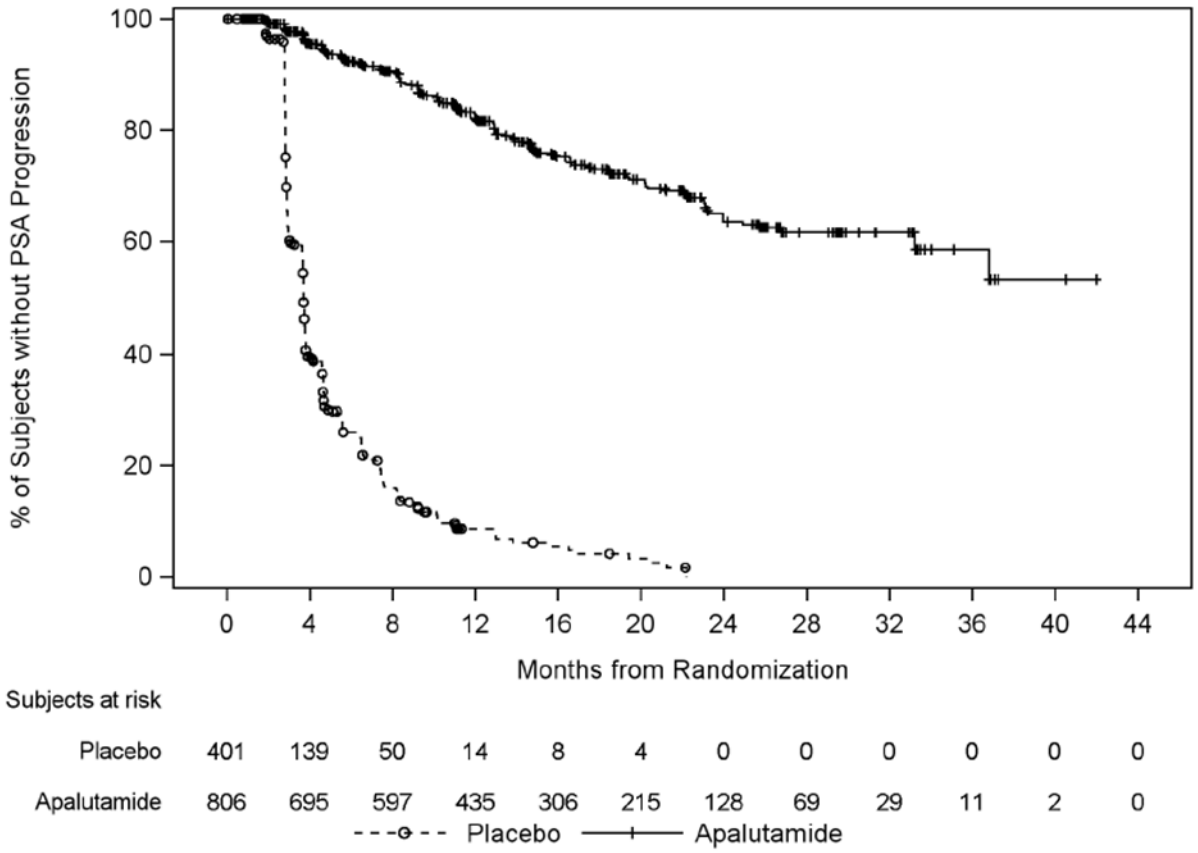
Furthermore, the Applicant provided the information on participants’ QoL with and without AEs for each AE and for each one of the 29 cycles of the study individually. There is still a lack of statistical information of overall changes in QoL in participants with and without AEs. The huge amount of information on different parameters of QoL during each one of study cycles, including answers of participants on each one of the study questions, does not allow to perform proper conclusion on differences between study arms.

Other Efficacy Endpoints- PSA Response

The PSA response rate was defined as the proportion of subjects who achieved ≥50% decline in PSA value from baseline assessed by a central laboratory according to PCWG2 criteria. The PSA response was confirmed by a

central laboratory measurement taken ≥4 weeks later. A confirmed PSA response was observed in 90% of subjects in the apalutamide arm and 2.2% of subjects in the placebo arm (Table 21; p<0.0001); total response (confirmed and unconfirmed) was observed in 93% and 3.5% of subjects, respectively. Subjects treated with apalutamide demonstrated a 40-fold improvement in PSA response over subjects treated with placebo.

Figure 12: Kaplan-Meier Plot of Time to PSA Progression; Intent-to-treat Population (Study ARN-509-003)



Other Efficacy Endpoints- Subsequent Therapy and PFS2

Table 28. Summary of First Subsequent Systemic Therapy for Prostate Cancer; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT population	401	806
Number of subjects with first subsequent systemic therapy for prostate cancer[a]	222 (55.4%)	175 (21.7%)
Hormonal	193 (86.9%)	154 (88.0%)
Abiraterone	161 (72.5%)	125 (71.4%)
Enzalutamide	28 (12.6%)	20 (11.4%)
Bicalutamide	3 (1.4%)	8 (4.6%)
Flutamide	1 (0.5%)	1 (0.6%)
Chemotherapy	19 (8.6%)	15 (8.6%)
Docetaxel	18 (8.1%)	15 (8.6%)
Cabazitaxel	1 (0.5%)	0
Other	10 (4.5%)	6 (3.4%)
Sipuleucel-T	9 (4.1%)	4 (2.3%)
Investigational Drug	0	1 (0.6%)
Radium Ra 223 Dichloride	0	1 (0.6%)
Dexamethasone	1 (0.5%)	0

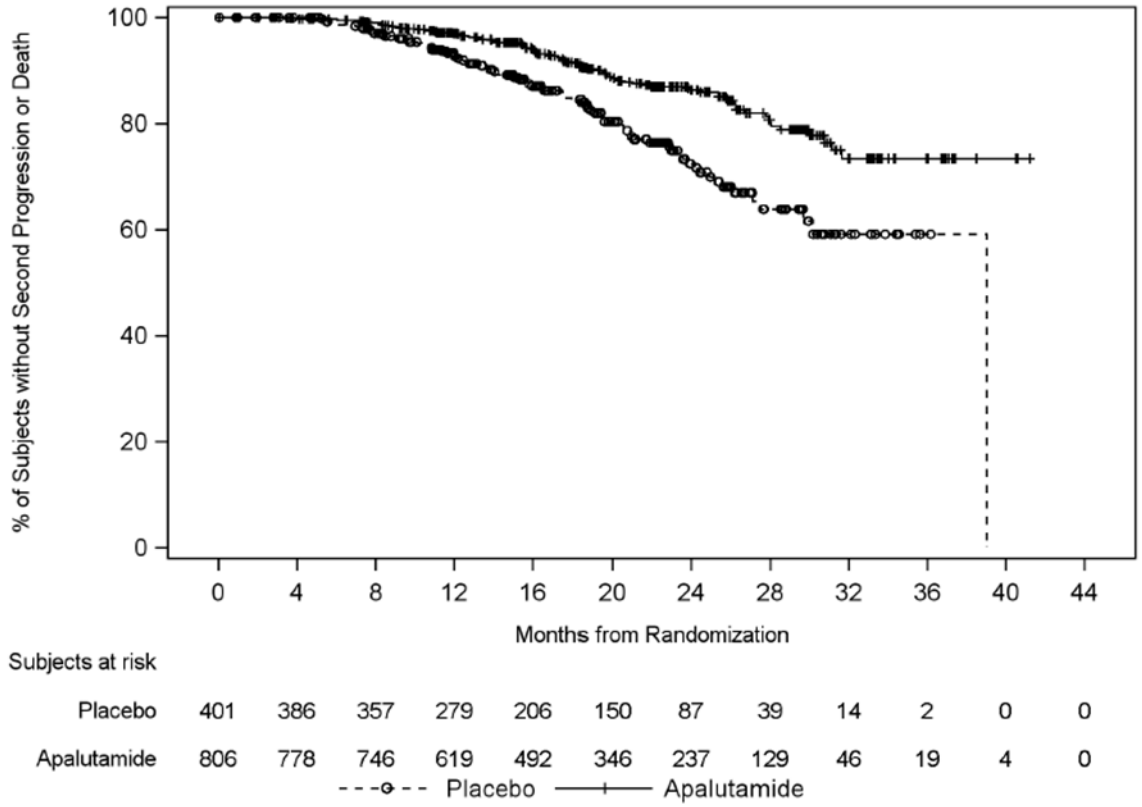
[a] Only for this row, percent is based on using the ITT population as denominator, all the following rows use this row as the denominator.
Note: Continuing ADT is not considered as a subsequent therapy.

Table 29. Summary of Second Progression-Free Survival (PFS2) – Non-stratified Analysis; Intent-to treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Event	78 (19.5%)	91 (11.3%)
Censored	323 (80.5%)	715 (88.7%)
PFS2 (months)		
25th percentile (95% CI)	22.97 (19.58, 25.53)	31.15 (28.06, NE)
Median (95% CI)	39.03 (30.16, 39.03)	NE (NE, NE)
75th percentile (95% CI)	39.03 (NE, NE)	NE (NE, NE)
Range	(0.0+, 39.0)	(0.0+, 41.2+)
12-month event-free rate (95% CI)	0.930 (0.898, 0.952)	0.970 (0.955, 0.980)
24-month event-free rate (95% CI)	0.725 (0.658, 0.781)	0.863 (0.829, 0.891)
36-month event-free rate (95% CI)	0.591 (0.487, 0.681)	0.734 (0.659, 0.796)
. p-value[a]		<.0001
Hazard ratio (95% CI) [b]		0.489 (0.361,0.662)

[a] p-value is from a non-stratified log-rank test
[b] Hazard ratio is from a non-stratified proportional hazards model with a single factor of treatment group. Hazard ratio < 1 favors active treatment.
Note: +=censored observation, NE=not estimable

Figure13: Kaplan-Meier Plot of Second Progression-Free Survival (PFS2); Intent-to-treat Population (Study ARN-509-003)



An overall updated PFS2 analysis was also conducted, based on an additional year of data collection since the original application with a CCO date of 17 May 2018. For the placebo arm, most subjects did receive approved therapies for mCRPC after their MFS event. Nonetheless, the apalutamide arm continued to be highly favored for PFS2, as defined by the time from randomization to progression with first subsequent anti-cancer therapy or death (PFS2) (HR=0.499; CI: 0.393, 0.632; p<0.0001). These results are consistent with the results from the initial analysis. PFS2 data continue to mature but there is no planned/required number of such events for any further formal analysis of this data.

Table 30. Summary of Second Progression-Free Survival (PFS2) – Non-stratified Analysis; Intent-to- treat Population (Study ARN-509-003)

ITT Population	Placebo 401	Apalutamide 806
Event	120 (29.9%)	162 (20.1%)
Censored	281 (70.1%)	644 (79.9%)
PFS2 (months)		
25th percentile (95% CI)	24.48 (21.91, 27.10)	34.92 (31.01, 38.41)
Median (95% CI)	39.33 (35.84, 49.94)	NE (NE, NE)
75th percentile (95% CI)	49.94 (46.88, 49.94)	NE (NE, NE)
Range	(0.0+, 49.9)	(0.0+, 51.6+)
12-month event-free rate (95% CI)	0.932 (0.902, 0.954)	0.970 (0.955, 0.980)
24-month event-free rate (95% CI)	0.763 (0.711, 0.807)	0.863 (0.836, 0.886)
36-month event-free rate (95% CI)	0.563 (0.489, 0.631)	0.740 (0.699, 0.776)
p-value[a]		<.0001
Hazard ratio (95% CI)[b]		0.499 (0.393, 0.632)

[a] p-value is from a non-stratified log-rank test
[b] Hazard ratio is from a non-stratified proportional hazards model with a single factor of treatment group. Hazard ratio < 1 favors active treatment.
Note: + = censored observation, NE = not estimable
[TEFPC22.RTF] [JNJ-56021927\ARN-509-003\DBR_EUREGUPD\RE_EUREGUPD\PROD\TEFPC22.SAS] 19JUN2018, 15:59

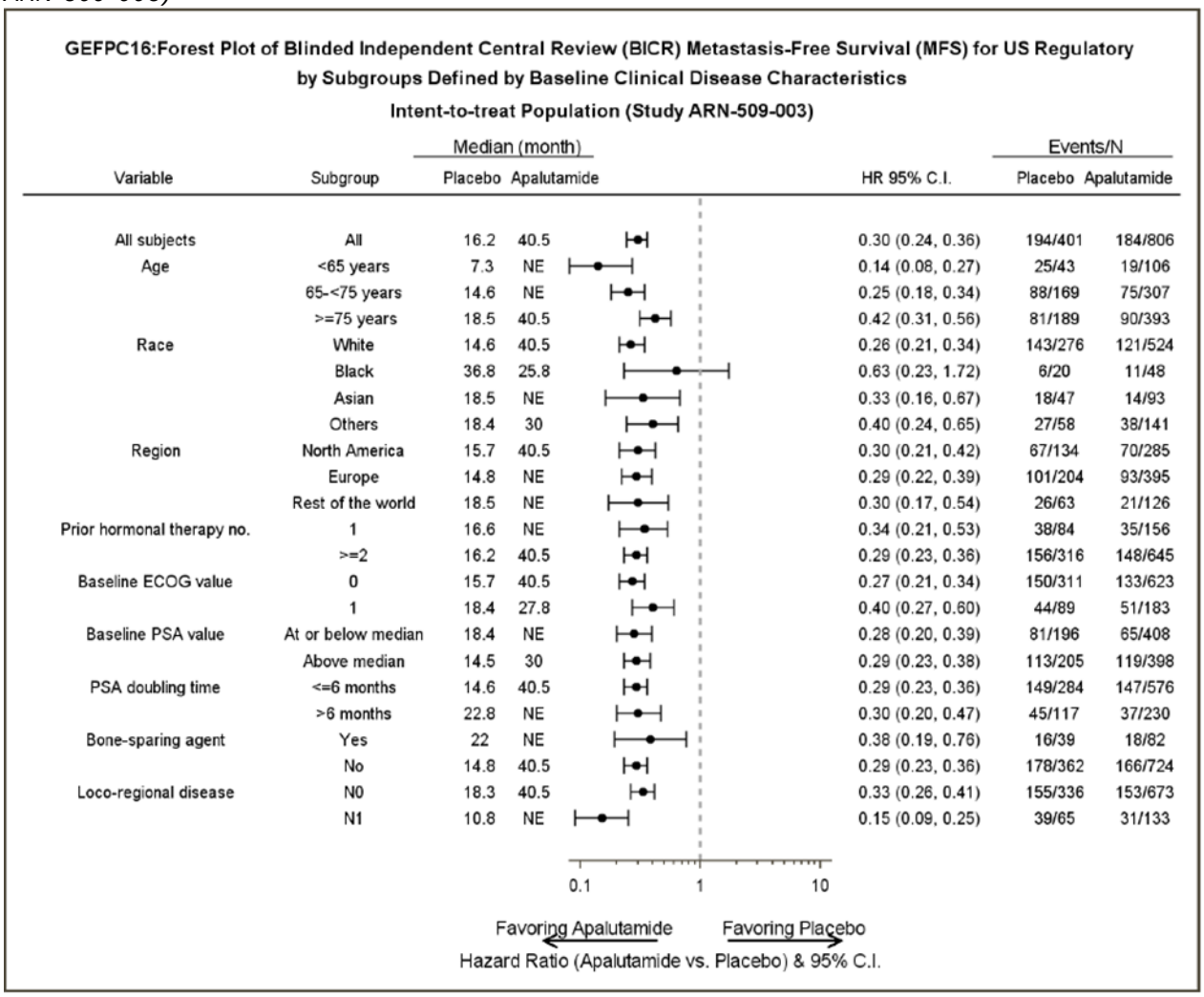
Biomarkers

Exploratory biomarker analysis was performed on blood samples collected at progression to identify markers of cross resistance to subsequent therapy. Because the ARV-7 splice variant of the AR is a potential mechanism of resistance for AR directed therapies, samples collected at the time of the first disease progression were tested for presence of ARV-7. ARV-7 was shown to occur in only 3 of 28 subjects (10.7%) with a progression sample that was tested in the apalutamide arm and 6 of 36 subjects (16.7%) with a progression sample that was tested in the placebo arm. In this population, duration on subsequent therapy in ARV-7 positive subjects was marginally shorter than ARV-7 negative subjects (24.9 months versus 28.5 months).

Ancillary analyses

Subgroup Analyses of Metastasis-Free Survival

Figure 12. Forest Plot of Blinded Independent Central Review (BICR) Metastasis-Free Survival (MFS) for US Regulatory by Subgroups Defined by Baseline Clinical Disease Characteristics Intent-totreat Population (Study ARN-509-003)



The treatment effect of apalutamide on MFS across all subgroups using ex-US censoring rules was consistent with the results above.

Summary of Metastasis-free Survival Analyses

All prespecified MFS analyses showed a significant treatment effect in favor of apalutamide compared with placebo (Table 41).

Table 31. Summary of Metastasis-free Survival Analyses

	Apalutamide Number of events n (%)	Apalutamide Median months (95% CI)	Placebo Number of events n (%)	Placebo Median Months (95% CI)	Hazard Ratio (95% CI)	p value
US Censoring Rules						
Independent Review (stratified)	184 (23)	40.5 (NE, NE)	194 (48)	16.2 (14.59,18.40)	0.280[b] (0.227, 0.346)	<0.0001[a]
Independent Review (non-stratified)	184 (23)	40.5 (NE, NE)	194 (48)	16.2 (14.59,18.40)	0.295[d] (0.240, 0.362)	<0.0001[c]
Independent Review (corrected stratification)	184 (23)	40.5 (NE, NE)	194 (48)	16.2 (14.59, 18.40)	0.286[b] (0.233, 0.352)	<0.0001[a]
Investigator Review (stratified)	189 (23)	41.2 (30.52, 41.20)	219 (55)	14.6 (11.10, 15.24)	0.251[b] (0.205, 0.308)	<0.0001[a]
Ex-US Censoring Rules						
Independent Review (stratified)	209 (26)	40.5 (29.70, 40.51)	210 (52)	15.7 (14.55,18.40)	0.297[b] (0.244, 0.362)	<0.0001[a]
Independent Review (non-stratified)	209 (26)	40.5 (29.70, 40.51)	210 (52)	15.7 (14.55,18.40)	0.310[d] (0.256, 0.377)	<0.0001[c]
Independent Review (corrected stratification)	209 (26)	40.5 (29.70, 40.51)	210 (52)	15.7 (14.55,18.40)	0.303[b] (0.249, 0.370)	<0.0001[a]
Investigator Review (stratified)	212 (26)	41.2 (30.03, 41.20)	231 (58)	14.6 (11.10, 15.24)	0.268[b] (0.221, 0.325)	<0.0001[a]

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio < 1 favors active treatment.
[c] p-value is from a non-stratified log-rank test
[d] Hazard ratio is from a non-stratified proportional hazards model with a single factor of treatment group. Hazard ratio < 1 favors active treatment.
NE= not estimable

Further characterization of MFS

In an exploratory multivariate analysis, the Cox proportional hazards model (with treatment in the model) was used to identify the following variables as the important favorable prognostic factors (p-value < 0.05) for MFS: PSA baseline ≤ 7.8 ng/mL; a PSADT >6 month; loco-regional disease status of N0; and Gleason Score ≤7.

Consequently, the late progressors are defined as having all 4 of the important favourable prognostic factors. The early progressors are defined as having all 4 of the following conditions: PSA baseline >7.8 ng/mL; a PSADT ≤6 months; loco-regional disease status of N1; and Gleason Score ≥8.

Subjects not defined as early or late are referred to as medium progressors.

The consistent significant treatment effect of apalutamide on MFS has been shown across the 3 progressor groups (early progressors: HR[95% CI]=0.142[0.048, 0.424] with a p-value of <0.0001; medium progressors: HR[95% CI]=0.304[0.248,0.374] with a p-value of <0.0001; late progressors: HR[95% CI]=0.263[0.101, 0.685] with a p-value of 0.0033). In addition, an exploratory interaction test between treatment and progressor type yielded a p-value of 0.1691, indicating that there is no significant heterogenous treatment effect of apalutamide among the 3 progressor groups.

Summary of main study(ies)

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

Table 32.Summary of Efficacy for trial ARN-509-003

Title: ARN-509-003 A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Apalutamide compared with placebo in subjects with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer.			
Study identifier	EudraCT Number: 2012-004322-24		
Design	Randomised (2:1) phase 3		
	Duration of main phase:		14 October 2013 – 19 May 2017 (DCO)
Hypothesis	Superiority		
Treatments groups	Apalutamide		240 mg per day, 806 patients randomised
	Placebo		Placebo, 401 patients randomised
Endpoints and definitions	Primary endpoint	MFS	Time from randomization to first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastases or death, whichever occurred first
	Secondary endpoint	Time to metastasis (TTM)	Time from randomization to first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis + 1 day.
	Secondary endpoint	Progression-free survival (PFS)	Time from randomization to first documentation of BICR-confirmed radiographic progressive disease or death+ 1 day.

	Secondary endpoint	Time to symptomatc progression	Time from date of randomization to date of documentation in the CRF of SRE, Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy or development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy + 1 day.
	Secondary endpoint	Time to initiation of cytotoxic chemothera py	Time from randomization to documentation of a new cytotoxic chemotherapy being administered to the patient + 1 day.
	Secondary endpoint	OS	Overall survival. Death any cause
Database lock	19 May 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Apalutamide	placebo
	Number of subject	806	401
	MFS (median; months)	40.51	15.70
	95%CI	(NE, NE)	(14.55, NE)
	TTM (median; months)	40.5	16.59
	95%CI	(NE, NE)	(14.59, 18.46)
	PFS (median; months)	40.51	14.72
	95%CI	(NE, NE)	(14.49, 18.37)
	Time to symptomatc progression (TTSP) (median; months)	NE	NE

	95%CI	(NE, NE)	(NE, NE)	
	Time to initiation of cytotoxic chemotherapy	NE	NE	
	95%CI	(NE, NE)	(NE, NE)	
	OS	NE	39.03	
	95%CI	(NE, NE)	(39.03, NE)	

Effect estimate per comparison	Primary endpoint: MFS	Comparison groups	Apalutamide vs placebo
		HR	0.280
		95%CI	(0.227, 0.346)
		P-value	< 0.0001
	Secondary endpoint: TTM	Comparison groups	Apalutamide vs placebo
		HR	0.271
		95%CI	(0.219, 0.335)
		P-value	< 0.0001
	Secondary endpoint: PFS	Comparison groups	Apalutamide vs placebo
		HR	0.291
		95%CI	(0.238, 0.356)
		P-value	< 0.0001
	Secondary endpoint: TTSP	Comparison groups	Apalutamide vs placebo
		HR	0.0.447
		95%CI	(0.315, 0.634)
		P-value	< 0.0001
	Secondary endpoint: Time to initiation of cytotoxic chemotherapy	Comparison groups	Apalutamide vs placebo
		HR	0.435
		95%CI	(0.286,0.661)
		P-value	< 0.0001
	OS	Comparison groups	Apalutamide vs placebo
		HR	0.700
		95%CI	(0.472, 1.038)
		P-value	0.0742
Notes			
Analysis description			

Table 33 - Summary of Blinded Independent Central Review (BICR) Results using ex-US Regulatory Censoring Rules – Stratified Analysis; Intent-to-treat Population (Study ARN-509-003)

	Placebo	Apalutamide
ITT Population	401	806
Metastasis-Free Survival (MFS)		
Event	210 (52.4%)	209 (25.9%)
Censored	191 (47.6%)	597 (74.1%)
MFS (months)		

25th percentile (95% CI)	7.26 (5.55, 7.43)	19.55 (18.23, 22.14)
Median (95% CI)	15.70 (14.55, 18.40)	40.51 (29.70, 40.51)
75th percentile (95% CI)	29.47 (23.06, 36.83)	40.51 (NE, NE)
Range	(0.0+, 36.8)	(0.0+, 40.5)
12-month event free rate (95% CI)	0.579 (0.525, 0.629)	0.861 (0.833, 0.884)
24-month event free rate (95% CI)	0.296 (0.235, 0.360)	0.682 (0.638, 0.722)
36-month event free rate (95% CI)	0.165 (0.055, 0.327)	0.514 (0.443, 0.581)
p-value[a]		<0.0001
Hazard ration (95% CI)[b]		0.297 (0.244, 0.362)
Time to Metastasis		
Event	191 (47.6%)	175 (21.7%)
Censored	210 (52.4%)	631 (78.3%)
Time to metastasis (months)		
25th percentile (95% CI)	7.29 (5.55, 7.45)	21.95 (18.89, 25.03)
Median (95% CI)	16.59 (14.59, 18.46)	40.51 (31.15, 40.51)
75th percentile (95% CI)	33.38 (23.46, 36.83)	40.51 (NE, NE)
Range	(0.0+, 36.8)	(0.0+, 40.5)
12-month event free rate (95% CI)	0.581 (0.526, 0.631)	0.869 (0.842, 0.892)
24-month event free rate (95% CI)	0.306 (0.243, 0.371)	0.701 (0.657, 0.740)
36-month event free rate (95% CI)	0.181 (0.061, 0.353)	0.557 (0.485, 0.623)
p-value[a]		<0.0001
Hazard ration (95% CI)[b]		0.279 (0.227, 0.342)
Progression-Free Survival		
Event	219 (54.6%)	220 (27.3%)
Censored	182 (45.4%)	586 (72.7%
PFS (months)		
25th percentile (95% CI)	7.20 (3.94, 7.36)	18.50 (16.59, 21.95)
Median (95% CI)	14.65 (11.27, 17.97)	40.51 (29.40, 40.51)
75th percentile (95% CI)	29.47 (22.38, 36.83)	40.51 (NE, NE)
Range	(0.0+, 36.8)	0.0+, 40.5)
12-month event free rate (95% CI)	0.543 (0.489, 0.593)	0.842 (0.813, 0.867)
24-month event free rate (95% CI)	0.287 (0.228, 0.350)	0.668 (0.628, 0.708)
36-month event free rate (95% CI)	0.158 (0.053, 0.315)	0.512 (0.443, 0.577)
p-value[a]		<0.0001
Hazard ration (95% CI)[b]		0.300 (0.247, 0.364)
Time to Cytotoxic Chemotherapy		
Event	44 (11.0%)	46 (5.7%)
Censored	357 (89.0%)	760 (94.3%)
Time to Cytotoxic Chemotherapy (months)		
25th percentile (95% CI)	34.10 (29.70, NE)	37.13 (32.59, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)

75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 39.5+)	(0.0+, 42.0+)
12-month event free rate (95% CI)	0.951 (0.924, 0.969)	0.991 (0.980, 0.996)
24-month event free rate (95% CI)	0.859 (0.807, 0.897)	0.928 (0.898, 0.949)
36-month event free rate (95% CI)	0.704 (0.528, 0.824)	0.814 (0.731, 0.873)
p-value[a]		<0.0001
Hazard ration (95% CI)[b]		0.435 (0.286, 0.661)

[a] p-value is from a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1).
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment arm, stratified by PSADT (≤6 months vs. >6 months), Bone-sparing agent use (Yes vs. No) and Loco-regional disease (N0 vs. N1). Hazard ratio <1 favors active treatment.
Note: +=censored observation, NE=not estimable

Analysis performed across trials (pooled analyses and meta-analysis)

Two studies were presented for the analysis of efficacy: pivotal phase III study ARN-509-003 and phase II study ARN-509-001. There was a difference in these studies both in the definition of high risk (PSADT ≤10 months for ARN-509-003 study and PSADT ≤10 months or PSA value ≥8 ng/mL within 3 months prior to enrollment for ARN-509-001 study) and in the primary outcome (MFS for ARN-509-003 study, but MFS is only secondary endpoint for the study ARN-509-001). Therefore, the direct comparison/meta-analysis of these studies was rather impossible.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	476	480	102

Supportive study(ies)

Supportive Phase II study ARN-509-001 included men with progressive advanced CRPC. Study population was similar to that of ARN-509-003 study. Study compared effects of three groups of participants: (1) participants with NM-CRPC (N=51, efficacy population N=47), (2) participants with mCRPC, not previously treated with ZYTIGA (N=25), and (3) participants with mCRPC previously treated with ZYTIGA (N=21). See table below (source: SCE provided by Applicant).

Four of the 51 subjects with NM-CRPC in Study ARN-509-001 had bone metastasis at baseline and were excluded from the efficacy analysis set (Cohort 1, N=47 efficacy population). Men were in high risk of NM CRPC defined as a PSADT ≤10 months or PSA value ≥8 ng/mL within 3 months prior to enrolment. Participants were treated with 240 mg apalutamide daily.

Table 33. ARN-509-001 Study

Study Number Phase	Study Design Study Population Primary Objective(s)	Treatment Regimen	Number of Subjects
ARN-509-001 **Phase 1/2**	Multicenter, first-in-human, dose-escalation, proof-of-concept study Patients with progressive advanced NM-CRPC[1] **Phase 1**: To assess the safety of apalutamide in subjects with progressive advanced CRPC, determine the MTD and/or RP2D **Phase 2**: To determine PSA response at 12 weeks per PCWG2 criteria (primary objective, all cohorts). To determine MFS[3] (a secondary objective specifically in Cohort 1: NM-CRPC)	**Phase 1**: Dose-escalation of apalutamide from 30 to 480 mg once daily continuous[4] **Phase 2:** Apalutamide 240 mg once daily continuous[4]	**Phase 1:** N=30 **Phase 2**: N=97 Cohort 1: NM-CRPC Enrolled subjects: N=51 Efficacy analysis set: N=47[6] Cohort 2: mCRPC treatment naive[7] N=25 Cohort 3: mCRPC previously treated with ZYTIGA[8] N=21

In this study MFS is defined as the time from the start of treatment until new metastatic lesions are observed on computed tomography/magnetic resonance imaging scans and/or radionuclide bone scans (according to PCWG2 criteria slightly modified to reflect tumor evaluations performed every 16 weeks) or death occurs, whichever is first. Subjects were to be discontinued from treatment for documented disease progression (PSA progression and radiographic progression or clinical progression alone), however, a large proportion of subjects discontinued treatment due to signs of disease progression that did not meet the radiographic progression endpoint.

At the time of the clinical cut-off date, 42 subjects (82%) from Cohort 1 discontinued treatment; treatment was ongoing for 9 (18%) subjects. The primary reasons for discontinuation of study treatment were disease progression (13 subjects, 26%), TEAEs (9 subjects, 18%), and “other” (7 subjects, 14%); “other” reasons were for unconfirmed progression. The median duration of treatment was 27 months for Cohort 1. PSA responses at 12 weeks showed treatment with apalutamide resulted in a 50% decline in PSA from baseline at Week 12 for 89% of subjects in Cohort 1. The PSA response rate at any time during Phase 2 of the study was 94% for subjects in Cohort 1. The median percent change at Week 12 was -85.4% (range: -99.9, 52.2).

Addition of supportive data from from Cohort 1 (NM-CRPC) of the Phase 2 portion of Study ARN-509-001 population may increase the total number of patients for analysis of efficacy, however, it should be kept in mind that difference in the baseline characteristics and different definition of high risk is a strong indication of the selection bias and has an impact on the efficacy results.

Besides definition of MFS in this supportive study and main study (ARN-509-001) was slightly different. In the main study MFS was defined as the time from randomization to first evidence of blinded independent central review-confirmed radiographically detectable bone or soft tissue distant metastasis or death due to any cause (whichever occurs earlier).

The demographic and baseline disease characteristics of subjects in study ARN-509-003 and the NM-CRPC cohort (Cohort 1) of study ARN-509-001 were mostly similar. However, subjects in study ARN-509-003, had a higher median age compared to subjects from Cohort 1 of study ARN-509-001 (74 years vs 71), with 26% of subjects 80 years of age or older compared with a median age 71 for. Additionally, subjects in study

ARN-509-003 had overall higher baseline tumor stages and were more likely to have a Gleason score >7 compared with subjects in Cohort 1 of study ARN-509-001.

Although results of efficacy analysis of this study seem to be supportive for the pivotal, ARN-509-003 study, the direct comparison and/or unification of these two studies is impossible due to different baseline characteristics of participants, different main objectives, different study designs and a small number of participants in the ARN-509-001 study.

2.5.3. Discussion on clinical efficacy

The company has submitted an application for marketing authorisation of apalutamide, a next generation, orally bioavailable, androgen receptor inhibitor, for the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease.

Apalutamide inhibits androgen receptor (AR) nuclear translocation and binding to the androgen response elements, resulting in the inhibition of downstream transcription of AR-regulated genes. Apalutamide is a potent and selective antagonist of the AR without significant agonist properties.

The proposed dose of apalutamide is 240 mg taken orally once-daily.

The current application is based on study ARN-509-003 (SPARTAN): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Apalutamide compared with placebo in subjects with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer. Supportive evidence comes from cohort 1 of the Phase 2 proportion of study ARN-509-001 in which 47 subjects with NM-CRPC have available efficacy data.

Key elements of study ARN-509-003 were discussed in several advices with the CHMP's SAWP and discussions were also held with national competent authorities (DK; ES, LT; UK). The CHMP agreed with the overall development approach, in particular endorsing trial population, placebo as comparator, primary and secondary endpoints and the analysis of biomarkers. It was emphasized that even if an improvement in MFS was observed, it would also be needed to understand the impact of treatment on survival of these patients, and in this regard, secondary endpoints such as Symprog and OS would become relevant during the decision making process.

Design and conduct of clinical studies

Focusing on the main study, the inclusion/exclusion criteria allowed the inclusion of patients on treatment with androgen deprivation therapy with a GnRH agonist/antagonist or prior bilateral orchiectomy, but castration resistant in terms of PSA progression (M0CRPC) at high risk as defined by PSADT < 10 months.

The definition of high-risk population seems to be the cause of treating them with apalutamide, given the high risk of developing metastases and eventually the potential impact on both, OS and QoL. There are no data whether apalutamide would be effective in a non-high risk NMCRPC.

The primary objectives of the study are clearly defined: to assess the efficacy of apalutamide compared with placebo in terms of MFS. From an individual-patient perspective and reasonably, from a clinical view the use of this variable is understood. However, study design will identify asymptomatic metastases in most of cases and in this regard the clinical value of apalutamide treatment was questioned. Other variables that could depict the clinical relevance of a mere delay in asymptomatic metastases are considered relevant when it comes to assessing the benefit risk balance of the proposed therapy, i.e. time to symptomatic progression or Overall survival.

Furthermore, multiple exploratory endpoints were defined, including biomarker analysis. This is endorsed as resistance to androgen therapy is eventually shown in the vast majority of prostate cancer patients. Due to the potential impact of apalutamide on next-line therapies, which in first-line of metastatic disease can include first-generation endocrine therapy (e.g., enzalutamide or abiraterone acetate), cross-resistance development is a possibility.

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

The sample size calculations were based on the expected amount of MFS events, the total number of planned interim analyses and OS median. This approach is considered adequate. An expected HR of 0.70 was used for calculations. Of note, the study was powered to find differences in OS.

The blind design of study, even supported, was probably risky taking into account the comparator arm and the PSA progression. Nevertheless, as the primary endpoint evaluated by a BICR, no major objections are raised.

Patients were randomized to a 2 (ARN-509): 1 (placebo) ratio using three stratification factors: PSADT, bone-Sparing agent use and loco-regional disease. Stratification factors are also agreed, although a region stratum should be included. In this regard, is reassuring that the subgroups analysis on MFS did not show important differences according to regions.

The phase 2 supportive study (ARN-509-001) included a cohort of patients with no metastatic disease (51 subjects enrolled; 47 subjects included in the efficacy analysis set). In Study ARN-509-001, high risk was defined as a PSADT ≤10 months or PSA value ≥8 ng/mL within 3 months prior to enrolment. The primary efficacy endpoint of the Phase 2 portion of Study ARN-509-001 was PSA response at 12 weeks according to the PCWG2 criteria.

Efficacy data and additional analyses

From the 2132 patients initially screened 925 were found ineligible and in the SPARTAN trial, between 14 Oct 2013 and 15 Dec 2016, 1207 patients were randomly assigned 2:1 to treatment with apalutamide (806 patients) or placebo (401 patients). A total of 332 study sites in 26 countries randomized patients in this study. The distribution of patients according to country could be an important factor to take into account at the time of assessing the impact of new hormonal agents (abiraterone) after progression, and as consequence on OS.

The data cut-off for the primary efficacy analysis was 19 May 2017. At that time 61% of subjects in the apalutamide arm and 30% of subjects in the placebo arm continued on study treatment. As of the 17 May 2018 clinical cutoff (CCO), 391 (48.7%) of subjects in the apalutamide arm still remain on treatment

The study protocol was amended eight times. Per amendment INT-6 (18-May-2015) study formulation changed from softgel capsules to tablets. Amendment INT-8 (15-March-2017) introduced changes in the hierarchical testing of secondary endpoints including re-estimation of time points for next analysis of symptomatic progression and other endpoints.

A total of 117 patients (9.7%) (9.2% in the apalutamide group and 9.9% in the placebo group) had major protocol deviations during the study. The most common protocol deviation was related to patients not fulfilling inclusion/exclusion criteria, although percentages are balanced between groups and no impact on study results is expected, the applicant was requested to further clarify the inclusion/exclusion criteria not met. After clarification, no specific trends were observed among major protocol deviations for inclusion/exclusion criteria.

Regarding baseline characteristics of trial population, median age at randomization was 74 years in both study arms. The great majority of patients were White (66.3%), 11.6% were Asian and 5.6% of trial population were Black or African American. The majority of patients had a baseline ECOG performance status 0 (77.4%). The median PSA DT was 4.40 months (range: 0.7 to 10.0 months) across treatment groups and most patients (71.3%) had PSADT ≤ 6 months.

No patient presented metastasis at diagnosis. Loco-regional disease (N1) was present in 16.4% of trial population according to patient distribution according to stratification factors. Some differences in the classification of patients according to baseline characteristics and distribution by stratification factors are noted.

One third of the population had previously received both surgery and radiotherapy. 99.5% of trial population had previously received hormonal therapy, being GnRHa (96.7%) and first generation antiandrogens the most frequently used (73.1%). Patients received none or 1 prior lines of prostate cancer therapy (1 prior lines: 7.9% in apalutamide and 8.0% in placebo received other prior prostate cancer therapy). Almost all patients received at least 1 prior hormonal therapy (99.5%), 21.0% in placebo arm and 19.5% in apalutamide received 1 prior hormonal therapy and 78.8% in placebo arm and 80.0% in apalutamide received ≥ 2 prior hormonal therapy. A minority, 1.7% and 2.1% in apalutaminde and placebo arms respectively had previously received chemotherapy. Prior treatments seem to be well balance between both groups.

More subjects needed a dose reduction and more subjects discontinued the treatment due to AE after first and after second dose reduction in apalutamide arm. Mean time to first dose reduction as well as time to discontinuation of treatment after the first dose reduction is shorter in apalutamide arm. Although the median time to second dose reduction and the time to discontinuation of the treatment after the second dose reduction are shorter in the apalutamide arm, the range of both these times is very wide showing a high dispersity of observed data. Therefore, it can be assumed that dose reduction and discontinuation due to AEs is related to apalutamide. A statistically significant difference between placebo and apalutamide arms for discontinuation because of adverse events was observed.

Results from SPARTAN trial in the efficacy target population of patients at the cut-off date of 19-May-2017 included the main analysis planned for MFS (BIRC assessed) and the first interim analysis for time to symptomatic progression (1 IA planned plus 1 final analyses), OS and time to cytotoxic chemotherapy (2 IA planned plus 1 final analysis for both).

With an event rate of 22.8% and 48.4% for apalutamide and placebo arms respectively, a statistically significant improvement in MFS was observed for apalutamide compared to placebo (HR: 0.280; 95% CI: 0.227, 0.346). The median MFS (95% CI) was 40.51 months (95% CI: NE, NE) in the apalutamide group and 16.20 months (95% CI: 14.59, 18.40) in the placebo group (Δ 24.3 months). Even when differences have been observed among reduction in bone, soft tissue and visceral metastases in apalutamide arm, all of them (reduction in bone, soft tissue and visceral metastases) showed relevant reduction in comparison with placebo arm. Most of the MFS events were due to appearance of metastases and only 9 patients in the apalutamide arm and 3 patients in placebo arms died without evidence of metastases. K-M curves showed an early and clear increasing separation form first tumour assessment (4 months) onwards with MFS event-free rates consistently favouring active treatment at different time points: event-free rate at 12 months: 87% in the apalutamide vs 59% in the placebo); at 24 months: 70% vs. 33%, respectively.

Two different analyses according to different censoring rules were submitted (US Regulatory censoring rules vs. ex-US Regulatory censoring rules) due to differing stratification approaches. Although the US Regulatory approach is considered the most conservative both show consistent results and no concerns arise. Main results are also supported by investigator assessment (HR: 0.251; 95% CI: 0.205, 0.308) and several sensitivity

analyses (upper limit of the 95% CI no greater than 0.310). The sensitivity analyses for secondary endpoints were also provided, giving similar results between analysis with both stratifications.

MFS showed consistent results across all subgroups analysed.

In an exploratory multivariate analysis, the Cox proportional hazards model (with treatment in the model) was used to identify the following variables as the important favorable prognostic factors (p-value < 0.05) for MFS: PSA baseline ≤ 7.8 ng/mL; a PSADT >6 month; loco-regional disease status of N0; and Gleason Score ≤7. However, as stratification during the randomization procedure was performed on PSADT (≤ 6 months vs. > 6 months), bone-sparing agent use (Yes vs. No) and loco-regional disease (N0 vs. N1), these covariates are not eligible to be included into multivariate analysis, as their distribution between study arms should be equal. The applicant's answered that the EMA regulations (2015) "Guideline on adjustment for baseline covariates in clinical trials" suggests that "The factors that are the basis of stratification should normally be included as covariates or stratification variables in the primary outcome model, except where stratification was done purely for an administrative reason". It is further noted that p-values for age, baseline ECOG value and number or prior hormonal therapies were not significant in the multivariate analysis. According to the MAA, this was because in predicting response, the effect of treatment with apalutamide was so strong that it was not impacted by ECOG status, age, or number of prior lines of therapy as predictors in the model.

Based on above mentioned multivariate analysis results, an additional analysis was provided by the applicant in order to assess whether there are any difference in efficacy outcomes (MFS) in patients who progressed early vs. late progressors. The early progressors were defined as having all 4 of the following conditions identified by exploratory multivariate analysis: (PSA baseline >7.8 ng/mL; a PSADT ≤6 months; loco-regional disease status of N1; and Gleason Score ≥8). Late progressors are defined as having all 4 of the identified important favourable prognostic factors (PSA baseline ≤ 7.8 ng/mL; a PSADT >6 month; loco-regional disease status of N0; and Gleason Score ≤7). Consistent treatment effect of apalutamide on MFS has been shown across the 3 progressor groups (early progressors: HR[95% CI]=0.142[0.048, 0.424]; medium progressors: HR[95% CI]=0.304[0.248,0.374]; late progressors: HR[95% CI]=0.263[0.101, 0.685]). The number of subjects in the early (15+23) and late progressors (38+60) groups were small as compared to

the medium progressor group (348+723).

Overall, secondary endpoints showed consistency with primary efficacy outcomes. Treatment with apalutamide delayed time to metastasis (TTM) (HR: 0.271; 95% CI: 0.219, 0.335) and PFS (HR: 0.291; 95% CI: 0.238,0.356). Consistency in both cases is not unexpected as these endpoints are closely related by definition. In the case of TTM only deaths events are excluded in comparison to MFS and in the case of PFS all radiological progressions are accounted.

More relevant are results in terms of time to symptomatic progression, OS and time to initiation of Cytotoxic Chemotherapy. Data on these three secondary endpoints comes from the first IA planned.

Despite data on time to symptomatic progression is still immature, event rate of 7.9% in apalutamide arm and 15.7% in placebo arm, results showed a HR: 0.447; 95% CI: 0.315,0.634 that crossed the pre-specified efficacy boundary for significance (p=0.00008) and thus this is to be considered the final analysis. Importantly, the definition of this endpoint included a composite of three different events: development of skeletal-related event, pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy, or development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy. Whereas an overall effect on the composite endpoint can be observed, when split by the different types of events no important differences are observed in the percentages of patients who experienced pain progression or worsening of disease –related symptoms only ((24/64) 37.5% in

apalutamide arm vs. (23/63) 36.5% in placebo arm) and it seems that differences are mainly due to skeletal-related events only ((15/ 64) 23.4% in apalutamide arm vs. (12/63) 19.0% in placebo arm) and more importantly loco-regional tumour progression only ((12/ 64) 18.8% in apalutamide arm vs. (17/63) 27% in placebo arm). However, the limited number of events translates small changes in absolute numbers into greater differences in relative numbers, reinforcing the need of more mature data on this endpoint.

Despite, the observed p-value (0.00000356) crossed the O'Brien-Fleming (OBF)-type efficacy boundary (p=0.00008) for significance and thus this will be the only analysis for time to symptomatic progression, the number of events cannot be considered enough in order to offer robust data. The applicant clarified that no statistical update is planned per the SAP. However, an updated exploratory analysis than does not involve further statistical testing was presented. This updated exploratory analysis is overall in line with the previous one, although no clinical relevant differences are observed in this endpoint between apalutamide and placebo arms.

OS data also still highly immature (event rate of 7.7% in apalutamide arm and 10.5% in placebo arm) did not cross the boundary for statistical significance (HR: 0.700, 95% CI: 0.472, 1.038) and although it appears that survival curves start to separate this does not allow any reliable conclusion regarding the potential benefit of apalutamide in the long-run. On the recommendation of the IDMC, study ARN-509-003 was unblinded and subjects who are randomized to placebo were given the option to receive apalutamide. Indeed, at the time of study unblinding, 104 subjects on the placebo arm were given the opportunity to cross over to apalutamide, 75 subjects went on to receive apalutamide. The Applicant is planning to thoroughly investigate cross-over adjusted sensitivity analysis only at the time of the next formal analysis of OS (2023). At time of the May 2018 CCO, OS data was still highly immature. OS events occurred in 19.0% (76) of subjects in the placebo arm patients and 15.4% (124) of subjects in the apalutamide arm. Median OS is not evaluable yet for apalutamide. As of 12 September 2018, overall survival (OS) events occurred in 22% (89) of subjects in the placebo arm and 17% (140) of subjects in the apalutamide arm. The next prespecified, formal statistical inferential analysis of OS is expected to take place when a total of 427 deaths have been observed. The current projection for the next CSR, which will include the updated OS data, will be available in June 2023.

At the time on DCO, 21.7% of patients in the apalutamide arm and 55.4% in the placebo arm received any subsequent systemic treatment for prostate cancer. Study protocol, recommended treatment with AA as first option for subsequent therapy if available. Accordingly, 71.4% and 72.5% of patients in apalutamide and placebo respectively received AA. Enzalutamide was received by 11.4% and 12.6% respectively arm who received any subsequent therapy.

PFS2 data (May 2017 cutoff), with 11.3% and 19.5% of events in apalutamide and placebo arms, showed an initial trend towards greater reduction of risk of disease progression with next line therapy or death for patients initially allocated to apalutamide arm compared to placebo (HR: 0.489, 95% CI: 0.361, 0.662). Updated data on PFS2 (May 2018 cutoff) were provided. This data seems to be in line with previous one. However, PFS2 is still immature, median of PFS2 in apalutamide is not evaluable yet. PFS2 events occurred in 29.9% (120) of subjects in the placebo arm patients and 20.1% (162) of subjects in the apalutamide arm. The Applicant commits to providing updated PFS2 data on an annual basis (eg, June of 2019, 2020, 2021, 2022)

Both time to symptomatic progression and OS can provide a good picture of the real benefit introducing apalutamide in the treatment of non-metastatic patients. Even though, both of them could indicate positive outcomes, there is an important drawback in the maturity of the data, even though and importantly no indication of detrimental effect on survival has been observed.

Results in terms of Time to Initiation of Cytotoxic Chemotherapy can provide the clinical management of patients once they progress and a delay in initiation of chemotherapy can be considered of relevant from a patient´s point of view. Results showed a numerical trend towards superiority of apalutamide treatment, however data is also considered too immature (event rate 5.7% vs. 11% in apalutamide and placebo arms) and the boundary for statistical significance was not either crossed in this IA.

Other secondary efficacy endpoints, PSA response rate (proportion of subjects who achieved ≥50% decline in PSA value from baseline) and time to PSA progression, supported primary efficacy results. A confirmed PSA response rate was observed in 89.7% of patients in apalutamide arm vs. 2.2% in placebo arm. The majority of patients (83.3%) in placebo arm had experienced PSA progression at the time of the analysis whereas only 23.8% of patients in apalutamide arm had experienced such event. Median time to PSA progression was 3.71 months in placebo arm whereas it was not reached in apalutamide arm. A clear and early separation of time to PSA curves can be observed.

QoL analyses, even if they do not appear to show a detrimental effect, they are not stressing any improvement either.

Finally, data on biomarkers is limited. An analysis of ARV7 a marker of resistance to AR therapies (RNA samples collected at end of first study treatment) was performed. Nine out of 96 (9.4%) subjects in the apalutamide arm and 13 out of 104 (12.5%) subjects in placebo arm expressed ARV7 at end of first treatment. Among the subset of subjects who had a PFS2 event, 3 out of 28 (10.7%) subjects in the apalutamide arm and 6 out of 36 (16.7%) subjects in the placebo arm were ARV7 positive. A formal statistical correlation was not performed as it would not be meaningful. However, PFS2 was observed to be marginally shorter for ARV7-positive subjects and with AR anomalies than ARV7-negative subjects (24.9 months to 28.5 months) or without AR anomalies (24.9 months to 29.7 months). However, as the number of subjects expressing ARV7 or other AR anomalies and who had had a PFS2 event was low, the analysis should be considered as exploratory. The Applicant is recommended to submit a subgroup analysis from the SPARTAN study, comparing MFS and PFS2 between subjects expressing AR anomalies versus those without AR anomalies.

Despite results from the SPARTAN trial have shown an unequivocal and clinically relevant effect in terms of delay of appearance of metastases or death compared to placebo, it still needs to be clarified to what extent these findings have an impact on long-term survival of patients. OS data is still immature so as to draw any firm conclusion and the immaturity of data regarding other potentially relevant secondary endpoints such as time to symptomatic progression or time to initiation of cytotoxic therapy precludes from drawing any firm conclusion. Importantly, the observed effect in the overall composite endpoint of time to symptomatic progression is not clear enough when the result is split into the different types of events.

Beyond the individual patient perspective, which is undoubtedly important, survival increase has not been shown yet in the new setting of M0 CRPC, although no detrimental effect has been observed. The clinical value of this strategy, i.e. moving forward a hormonal therapy similar to those already authorized in first-line of metastatic setting, is not totally known, even though PFS2 data seem to offer some insights.

2.5.4. Conclusions on the clinical efficacy

The use of apalutamide seems to offer an important delay in the onset of metastases, which for the time being appears to be supported by important secondary endpoints such as PFS2. To date, the immature OS data have not shown a detrimental effect, which reaffirms the clinical benefit or apalutamide in this setting. Thus, the efficacy is considered sufficiently demonstrated. Updated data are warranted in order to further substantiate the benefit of this treatment.

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

PAES: In order to further evaluate the efficacy of Erleada, the MAH should submit the final clinical study report, including overall survival results, from study ARN-509-003 (SPARTAN) comparing the efficacy and safety of Apalutamide vs. placebo in subjects with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer.

2.6. Clinical safety

The safety of 240 mg of apalutamide plus ADT in the treatment of men with NM-CRPC is supported primarily by data from Study ARN-509-003, a multicenter, randomized, double-blind, placebo-controlled study of apalutamide or placebo with ADT background therapy in 1,201 treated subjects (apalutamide arm: 803 subjects; placebo arm: 398 subjects). Safety data from the pivotal Phase 3 Study ARN-509-003 were integrated with safety data from subjects who received 240 mg of apalutamide in 2 smaller studies which included both NM-CRPC and metastatic CRPC (mCRPC) subjects (Phase 1/2 Study ARN-509-001 [100 subjects] and Phase 1b Study 56021927PCR1019 [45 subjects]).

Table 34. Subjects treated in studies contributing to the Summary of Clinical Safety for apalutamide

Protocol Number	Study Phase Study Design Study Population	Treatment	Subjects Treated With 240 mg Apalutamide Daily Dose	Location of Clinical Study Report Data Cutoff Date
Integrated Analyses				
ARN-509-003	Phase 3 Multicenter, randomized, double-blind, placebo-controlled Men with NM-CRPC	apalutamide 240 mg once daily or matched placebo	803	Mod5.3.5.1\ARN-509-003 19 May 2017
ARN-509-001	Phase 1/2 Open-label, dose-escalation and proof-of-concept Men with progressive advanced CRPC	Dose Escalation (Phase 1)[a] Dose Expansion (Phase 2): apalutamide 240 mg daily	100 Phase 1: 3 subjects; Phase 2: 97 subjects	2015 Clinical Study Report: Mod5.3.3.2\ARN-509-001\2015 31 December 2014 2017 Clinical Study Report: Mod5.3.3.2\ARN-509-001\2017 31 March 2017
56021927PCR1019	Phase 1b Open-label, QT/QTc Men with CRPC	apalutamide 240 mg once daily	45	Mod5.3.4.2\56021927PCR1019 20 September 2016

[a] apalutamide doses of 30 mg, 60 mg, 90 mg, 120 mg, 180 mg, 240 mg, 300 mg, 390 mg, and 480 mg daily. Only subjects treated with the 240 mg dose contributed safety data to this summary.
CRPC=castration-resistant prostate cancer; NM-CRPC=non-metastatic castration-resistant prostate cancer; QTc=QT interval corrected for heart rate

Patient exposure

As of the data cut-off date for Study ARN-509-003, 61% of subjects in the apalutamide arm and 30% of subjects in the placebo arm were still receiving study treatment (Table 36).

Table 35. Treatment Disposition; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Subjects with treatment ongoing[a]	119 (29.9%)	489 (60.9%)	12 (12.0%)	32 (71.1%)	533 (56.2%)
Subjects discontinued from treatment	279 (70.1%)	314 (39.1%)	88 (88.0%)	13 (28.9%)	415 (43.8%)
Reason for termination					
Progressive disease	210 (52.8%)	155 (19.3%)	30 (30.0%)	12 (26.7%)	197 (20.8%)
Adverse event	25 (6.3%)	86 (10.7%)	15 (15.0%)	0	101 (10.7%)
Withdrawal by subject	39 (9.8%)	54 (6.7%)	9 (9.0%)	1 (2.2%)	64 (6.8%)
Other	2 (0.5%)	9 (1.1%)	15 (15.0%)	0	24 (2.5%)
Physician decision	NAP	NAP	9 (9.0%)	0	9 (0.9%)
Initiation of new anti-cancer therapy	NAP	NAP	8 (8.0%)	NAP	8 (0.8%)
Noncompliance with study procedures	0	6 (0.7%)	0	0	6 (0.6%)
Lost to follow-up	1 (0.3%)	1 (0.1%)	2 (2.0%)	0	3 (0.3%)
Protocol violation	2 (0.5%)	3 (0.4%)	NAP	0	3 (0.3%)

Key: NAP = not applicable
[a]Reflects the status on the data cutoff dates of the related studies.

Table 36. Summary of Cumulative Exposure; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Treatment Duration (months)[a]					
N	398	803	100	45	948
>= 0	398 (100.0%)	803 (100.0%)	100 (100.0%)	45 (100.0%)	948 (100.0%)
>= 4	348 (87.4%)	718 (89.4%)	87 (87.0%)	29 (64.4%)	834 (88.0%)
>= 8	256 (64.3%)	651 (81.1%)	70 (70.0%)	1 (2.2%)	722 (76.2%)
>= 12	178 (44.7%)	563 (70.1%)	57 (57.0%)	0	620 (65.4%)
>= 16	115 (28.9%)	428 (53.3%)	48 (48.0%)	0	476 (50.2%)
>= 20	69 (17.3%)	319 (39.7%)	47 (47.0%)	0	366 (38.6%)
>= 24	44 (11.1%)	206 (25.7%)	39 (39.0%)	0	245 (25.8%)
>= 28	20 (5.0%)	125 (15.6%)	31 (31.0%)	0	156 (16.5%)
>= 32	5 (1.3%)	46 (5.7%)	28 (28.0%)	0	74 (7.8%)
>= 36	1 (0.3%)	21 (2.6%)	25 (25.0%)	0	46 (4.9%)

[a]Treatment duration is defined as the duration from the date of the first dose of study drug to the date of last dose of study drug+1 divided by 30.4375.

Table 37. Summary of Dose Adjustment; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Number of dose level reduction					
0	339 (85.2%)	635 (79.1%)	91 (91.0%)	42 (93.3%)	768 (81.0%)
1	14 (3.5%)	66 (8.2%)	7 (7.0%)	3 (6.7%)	76 (8.0%)
2	45 (11.3%)	102 (12.7%)	2 (2.0%)	0	104 (11.0%)
Reason for Dose level reduction					
Adverse Event	13 (3.3%)	90 (11.2%)	7 (7.0%)	2 (4.4%)	99 (10.4%)
Other	46 (11.6%)	78 (9.7%)	2 (2.0%)	1 (2.2%)	81 (8.5%)
Number of dose level reduction due to AE					
0	385 (96.7%)	713 (88.8%)	93 (93.0%)	43 (95.6%)	849 (89.6%)
1	4 (1.0%)	45 (5.6%)	5 (5.0%)	2 (4.4%)	52 (5.5%)
2	9 (2.3%)	45 (5.6%)	2 (2.0%)	0	47 (5.0%)
Reason for Dose interruption					
Adverse Event	77 (19.3%)	270 (33.6%)	32 (32.0%)	5 (11.1%)	307 (32.4%)
Other	188 (47.2%)	346 (43.1%)	2 (2.0%)	2 (4.4%)	350 (36.9%)
Number of dose interruption due to AE					
0	321 (80.7%)	533 (66.4%)	68 (68.0%)	40 (88.9%)	641 (67.6%)
1	50 (12.6%)	176 (21.9%)	21 (21.0%)	4 (8.9%)	201 (21.2%)
2	21 (5.3%)	53 (6.6%)	8 (8.0%)	1 (2.2%)	62 (6.5%)
3	4 (1.0%)	27 (3.4%)	2 (2.0%)	0	29 (3.1%)
>3	2 (0.5%)	14 (1.7%)	1 (1.0%)	0	15 (1.6%)

Note: Dose level reduction is determined from the exposure page of the CRF. If a subject had a dose reduction due to AE and due to other reason, the subject is counted in "Dose level reduction due to AE" row.
Similar approach is used for subject counts in "Reason for dose interruption".

Adverse events

Table 38. Overall Safety Profile; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR 1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Subjects with 1 or more:					
TEAEs	371 (93.2%)	775 (96.5%)	100 (100.0%)	37 (82.2%)	912 (96.2%)
Related TEAEs[a]	216 (54.3%)	565 (70.4%)	88 (88.0%)	23 (51.1%)	676 (71.3%)
Grade 3-4 TEAEs	136 (34.2%)	362 (45.1%)	47 (47.0%)	10 (22.2%)	419 (44.2%)
Related TEAEs[a]	17 (4.3%)	113 (14.1%)	9 (9.0%)	3 (6.7%)	125 (13.2%)
Serious TEAEs[b]	92 (23.1%)	199 (24.8%)	32 (32.0%)	5 (11.1%)	236 (24.9%)
Related serious TEAEs[a]	6 (1.5%)	31 (3.9%)	0	0	31 (3.3%)
Grade 3-4 serious TEAEs	76 (19.1%)	150 (18.7%)	25 (25.0%)	5 (11.1%)	180 (19.0%)
TEAEs leading to treatment discontinuation	28 (7.0%)	85 (10.6%)	16 (16.0%)	0	101 (10.7%)
Related TEAEs[a]	8 (2.0%)	58 (7.2%)	6 (6.0%)	0	64 (6.8%)
TEAEs leading to death	1 (0.3%)	10 (1.2%)	1 (1.0%)	0	11 (1.2%)
Related TEAEs[a]	0	1 (0.1%)	0	0	1 (0.1%)
All deaths on treatment[c]	1 (0.3%)	10 (1.2%)	1 (1.0%)	0	11 (1.2%)
Adverse event	1 (0.3%)	7 (0.9%)	0	0	7 (0.7%)
Death due to prostate cancer	0	3 (0.4%)	1 (1.0%)	0	4 (0.4%)
Other	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019 are considered as on treatment death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. For each category, subjects are counted only once, even if they experienced multiple events in that category.

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Common Adverse Events

Table 4039. Number of subjects with Treatment-emergent Adverse events with Frequency of at Least 5% in Combined Apalutamide Group by System Organ Class and Preferred Term; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Subjects with 1 or more TEAEs	371 (93.2%)	775 (96.5%)	100 (100.0%)	37 (82.2%)	912 (96.2%)
System organ class					
Preferred term					
Gastrointestinal disorders	232 (58.3%)	468 (58.3%)	82 (82.0%)	15 (33.3%)	565 (59.6%)
Diarrhoea	60 (15.1%)	163 (20.3%)	41 (41.0%)	6 (13.3%)	210 (22.2%)
Nausea	63 (15.8%)	145 (18.1%)	42 (42.0%)	5 (11.1%)	192 (20.3%)
Constipation	52 (13.1%)	87 (10.8%)	17 (17.0%)	5 (11.1%)	109 (11.5%)
Abdominal pain	34 (8.5%)	65 (8.1%)	24 (24.0%)	0	89 (9.4%)
Dyspepsia	22 (5.5%)	58 (7.2%)	10 (10.0%)	0	68 (7.2%)
Vomiting	24 (6.0%)	44 (5.5%)	15 (15.0%)	1 (2.2%)	60 (6.3%)
Abdominal pain upper	32 (8.0%)	44 (5.5%)	11 (11.0%)	0	55 (5.8%)
Abdominal discomfort	22 (5.5%)	37 (4.6%)	11 (11.0%)	0	48 (5.1%)
General disorders and administration site conditions	158 (39.7%)	401 (49.9%)	79 (79.0%)	20 (44.4%)	500 (52.7%)
Fatigue	84 (21.1%)	244 (30.4%)	61 (61.0%)	18 (40.0%)	323 (34.1%)
Asthenia	33 (8.3%)	89 (11.1%)	9 (9.0%)	0	98 (10.3%)
Oedema peripheral	29 (7.3%)	69 (8.6%)	16 (16.0%)	3 (6.7%)	88 (9.3%)
Musculoskeletal and connective tissue disorders	159 (39.9%)	370 (46.1%)	65 (65.0%)	13 (28.9%)	448 (47.3%)
Arthralgia	30 (7.5%)	128 (15.9%)	25 (25.0%)	3 (6.7%)	156 (16.5%)
Back pain	59 (14.8%)	101 (12.6%)	25 (25.0%)	7 (15.6%)	133 (14.0%)
Pain in extremity	20 (5.0%)	73 (9.1%)	17 (17.0%)	1 (2.2%)	91 (9.6%)
Musculoskeletal pain	16 (4.0%)	38 (4.7%)	14 (14.0%)	2 (4.4%)	54 (5.7%)
Musculoskeletal chest pain	16 (4.0%)	36 (4.5%)	12 (12.0%)	0	48 (5.1%)
Infections and infestations	146 (36.7%)	342 (42.6%)	48 (48.0%)	5 (11.1%)	395 (41.7%)
Nasopharyngitis	25 (6.3%)	78 (9.7%)	16 (16.0%)	0	94 (9.9%)
Urinary tract infection	38 (9.5%)	63 (7.8%)	13 (13.0%)	3 (6.7%)	79 (8.3%)
Upper respiratory tract infection	21 (5.3%)	44 (5.5%)	13 (13.0%)	0	57 (6.0%)
Skin and subcutaneous tissue disorders	64 (16.1%)	316 (39.4%)	40 (40.0%)	9 (20.0%)	365 (38.5%)
Rash	13 (3.3%)	87 (10.8%)	11 (11.0%)	2 (4.4%)	100 (10.5%)
Pruritus	6 (1.5%)	50 (6.2%)	9 (9.0%)	1 (2.2%)	60 (6.3%)
Nervous system disorders	90 (22.6%)	288 (35.9%)	57 (57.0%)	6 (13.3%)	351 (37.0%)
Headache	25 (6.3%)	76 (9.5%)	15 (15.0%)	1 (2.2%)	92 (9.7%)
Dizziness	25 (6.3%)	75 (9.3%)	13 (13.0%)	1 (2.2%)	89 (9.4%)
Dysgeusia	6 (1.5%)	57 (7.1%)	16 (16.0%)	2 (4.4%)	75 (7.9%)
Vascular disorders	117 (29.4%)	319 (39.7%)	27 (27.0%)	3 (6.7%)	349 (36.8%)
Hypertension	79 (19.8%)	199 (24.8%)	8 (8.0%)	1 (2.2%)	208 (21.9%)
Hot flush	34 (8.5%)	113 (14.1%)	16 (16.0%)	2 (4.4%)	131 (13.8%)
Metabolism and nutrition disorders	82 (20.6%)	272 (33.9%)	37 (37.0%)	15 (33.3%)	324 (34.2%)
Decreased appetite	35 (8.8%)	99 (12.3%)	16 (16.0%)	11 (24.4%)	126 (13.3%)
Hypercholesterolaemia	6 (1.5%)	49 (6.1%)	8 (8.0%)	0	57 (6.0%)
Hyperglycaemia	15 (3.8%)	46 (5.7%)	6 (6.0%)	1 (2.2%)	53 (5.6%)
Renal and urinary disorders	142 (35.7%)	245 (30.5%)	43 (43.0%)	5 (11.1%)	293 (30.9%)
Haematuria	40 (10.1%)	65 (8.1%)	12 (12.0%)	2 (4.4%)	79 (8.3%)
Pollakiuria	34 (8.5%)	46 (5.7%)	14 (14.0%)	1 (2.2%)	61 (6.4%)
Urinary incontinence	15 (3.8%)	42 (5.2%)	6 (6.0%)	0	48 (5.1%)
Respiratory, thoracic and mediastinal disorders	79 (19.8%)	222 (27.6%)	48 (48.0%)	8 (17.8%)	278 (29.3%)
Dyspnoea	16 (4.0%)	65 (8.1%)	14 (14.0%)	6 (13.3%)	85 (9.0%)
Cough	28 (7.0%)	58 (7.2%)	19 (19.0%)	1 (2.2%)	78 (8.2%)
Investigations	62 (15.6%)	222 (27.6%)	36 (36.0%)	9 (20.0%)	267 (28.2%)
Weight decreased	25 (6.3%)	129 (16.1%)	13 (13.0%)	4 (8.9%)	146 (15.4%)

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Injury, poisoning and procedural complications	70 (17.6%)	230 (28.6%)	29 (29.0%)	1 (2.2%)	260 (27.4%)
Fall	36 (9.0%)	125 (15.6%)	9 (9.0%)	1 (2.2%)	135 (14.2%)
Psychiatric disorders	53 (13.3%)	145 (18.1%)	26 (26.0%)	3 (6.7%)	174 (18.4%)
Insomnia	21 (5.3%)	55 (6.8%)	10 (10.0%)	1 (2.2%)	66 (7.0%)
Blood and lymphatic system disorders	33 (8.3%)	86 (10.7%)	25 (25.0%)	6 (13.3%)	117 (12.3%)
Anaemia	16 (4.0%)	52 (6.5%)	17 (17.0%)	3 (6.7%)	72 (7.6%)
Endocrine disorders	8 (2.0%)	55 (6.8%)	16 (16.0%)	1 (2.2%)	72 (7.6%)
Hypothyroidism	5 (1.3%)	49 (6.1%)	15 (15.0%)	0	64 (6.8%)

Key: TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 19.1.

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Adverse events of grade 3 or 4

Hypertension and skin rash were the most frequently reported Grade 3 AEs in Study ARN-509-003 (≥3% of subjects in either of the treatment arms). No individual Grade 4 AE was reported for ≥1% of subjects in either ARN-509-003 treatment arm, or in the combined apalutamide group.

Skin rash was reported as a Grade 3 event for 42 subjects (5.2%) in the apalutamide arm and for 1 subject (0.3%) in the placebo arm (combined apalutamide group: 46 subjects [4.9%]). No Grade 3 events were reported for the AEs of special interest of seizure and hypothyroidism; Grade 3 events of fall and fracture were each reported for <3% of subjects in either ARN-509-003 treatment arm. No individual Grade 4 AE was reported for ≥1% of subjects in either ARN-509-003 treatment arm, or in the combined apalutamide group.

Table 40. Number of subjects with Treatment-Emergent Grade 3-4 Adverse Events with frequency of at least 1% in any treatment group by System Organ Class, Preferred Term, and toxicity grade (Safety population – Study ARN-509-003)

	Placebo			Apalutamide		
	Total	3	4	Total	3	4
Safety Population	398			803		
Subjects with 1 or more TEAEs	136 (34.2%)	128 (32.2%)	8 (2.0%)	362 (45.1%)	339 (42.2%)	23 (2.9%)
System organ class Preferred term						
Vascular disorders	50 (12.6%)	50 (12.6%)	0	122 (15.2%)	122 (15.2%)	0
Hypertension	47 (11.8%)	47 (11.8%)	0	115 (14.3%)	115 (14.3%)	0
Infections and infestations	12 (3.0%)	12 (3.0%)	0	52 (6.5%)	46 (5.7%)	6 (0.7%)
Urinary tract infection	4 (1.0%)	4 (1.0%)	0	10 (1.2%)	10 (1.2%)	0
Pneumonia	3 (0.8%)	3 (0.8%)	0	9 (1.1%)	8 (1.0%)	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.3%)	1 (0.3%)	0	50 (6.2%)	50 (6.2%)	0
Rash maculo-papular	0	0	0	15 (1.9%)	15 (1.9%)	0
Rash	1 (0.3%)	1 (0.3%)	0	10 (1.2%)	10 (1.2%)	0
Renal and urinary disorders	39 (9.8%)	37 (9.3%)	2 (0.5%)	38 (4.7%)	34 (4.2%)	4 (0.5%)
Haematuria	8 (2.0%)	7 (1.8%)	1 (0.3%)	13 (1.6%)	12 (1.5%)	1 (0.1%)
Acute kidney injury	6 (1.5%)	5 (1.3%)	1 (0.3%)	7 (0.9%)	6 (0.7%)	1 (0.1%)
Hydronephrosis	11 (2.8%)	11 (2.8%)	0	7 (0.9%)	7 (0.9%)	0
Urinary retention	9 (2.3%)	9 (2.3%)	0	7 (0.9%)	5 (0.6%)	2 (0.2%)
Renal failure	4 (1.0%)	4 (1.0%)	0	2 (0.2%)	2 (0.2%)	0
Urinary tract obstruction	5 (1.3%)	5 (1.3%)	0	2 (0.2%)	2 (0.2%)	0
Nervous system disorders	11 (2.8%)	11 (2.8%)	0	37 (4.6%)	36 (4.5%)	1 (0.1%)
Syncope	4 (1.0%)	4 (1.0%)	0	17 (2.1%)	17 (2.1%)	0
Injury, poisoning and procedural complications	6 (1.5%)	6 (1.5%)	0	33 (4.1%)	32 (4.0%)	1 (0.1%)
Fall	3 (0.8%)	3 (0.8%)	0	14 (1.7%)	14 (1.7%)	0
Cardiac disorders	11 (2.8%)	9 (2.3%)	2 (0.5%)	28 (3.5%)	23 (2.9%)	5 (0.6%)
Atrial fibrillation	3 (0.8%)	3 (0.8%)	0	9 (1.1%)	8 (1.0%)	1 (0.1%)
Investigations	5 (1.3%)	5 (1.3%)	0	21 (2.6%)	21 (2.6%)	0
Weight decreased	1 (0.3%)	1 (0.3%)	0	9 (1.1%)	9 (1.1%)	0
Musculoskeletal and connective tissue disorders	13 (3.3%)	13 (3.3%)	0	19 (2.4%)	19 (2.4%)	0
Back pain	6 (1.5%)	6 (1.5%)	0	6 (0.7%)	6 (0.7%)	0
Blood and lymphatic system disorders	6 (1.5%)	6 (1.5%)	0	17 (2.1%)	13 (1.6%)	4 (0.5%)
Anaemia	4 (1.0%)	4 (1.0%)	0	6 (0.7%)	6 (0.7%)	0
Eye disorders	6 (1.5%)	6 (1.5%)	0	14 (1.7%)	14 (1.7%)	0
Cataract	4 (1.0%)	4 (1.0%)	0	11 (1.4%)	11 (1.4%)	0

Key: TEAE=treatment-emergent adverse event.
Note: Percent is based on the Safety population.
Note: Table does not include Grade 5 events.
Note: Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity grade is used. If a subject has all adverse events with missing toxicity grades, the subject is only counted in the total column.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities Version 19.1.
Note: Toxicity Grade is based on NCI common toxicity criteria, version 4.0.
Note: Total is the sum of Grade 3 and 4.

Adverse events of special interest

Table 41. Treatment-emergent Adverse Events of Special Interest by Preferred Term; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Subjects with 1 or more TEAEs of special interest	72 (18.1%)	338 (42.1%)	46 (46.0%)	4 (8.9%)	388 (40.9%)
Special interest					
Preferred term					
Skin rash	22 (5.5%)	191 (23.8%)	25 (25.0%)	3 (6.7%)	219 (23.1%)
Rash	13 (3.3%)	87 (10.8%)	11 (11.0%)	2 (4.4%)	100 (10.5%)
Rash maculo-papular	2 (0.5%)	43 (5.4%)	3 (3.0%)	0	46 (4.9%)
Rash generalised	1 (0.3%)	19 (2.4%)	7 (7.0%)	1 (2.2%)	27 (2.8%)
Urticaria	1 (0.3%)	16 (2.0%)	1 (1.0%)	0	17 (1.8%)
Rash macular	1 (0.3%)	10 (1.2%)	3 (3.0%)	0	13 (1.4%)
Rash pruritic	2 (0.5%)	11 (1.4%)	0	0	11 (1.2%)
Conjunctivitis	0	7 (0.9%)	2 (2.0%)	0	9 (0.9%)
Rash papular	1 (0.3%)	4 (0.5%)	1 (1.0%)	0	5 (0.5%)
Skin exfoliation	0	4 (0.5%)	1 (1.0%)	0	5 (0.5%)
Erythema multiforme	0	4 (0.5%)	0	0	4 (0.4%)
Rash erythematous	0	3 (0.4%)	1 (1.0%)	0	4 (0.4%)
Drug eruption	1 (0.3%)	2 (0.2%)	1 (1.0%)	0	3 (0.3%)
Genital rash	0	3 (0.4%)	0	0	3 (0.3%)
Mouth ulceration	1 (0.3%)	2 (0.2%)	1 (1.0%)	0	3 (0.3%)
Rash pustular	0	2 (0.2%)	1 (1.0%)	0	3 (0.3%)
Stomatitis	1 (0.3%)	3 (0.4%)	0	0	3 (0.3%)
Blister	1 (0.3%)	1 (0.1%)	1 (1.0%)	0	2 (0.2%)
Dermatitis exfoliative	0	0	1 (1.0%)	0	1 (0.1%)
Papule	0	1 (0.1%)	0	0	1 (0.1%)
Pemphigoid	1 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Skin erosion	0	1 (0.1%)	0	0	1 (0.1%)
Rash vesicular	1 (0.3%)	0	0	0	0
Fall	36 (9.0%)	125 (15.6%)	9 (9.0%)	1 (2.2%)	135 (14.2%)
Fall	36 (9.0%)	125 (15.6%)	9 (9.0%)	1 (2.2%)	135 (14.2%)
Fracture	26 (6.5%)	94 (11.7%)	11 (11.0%)	0	105 (11.1%)
Rib fracture	14 (3.5%)	29 (3.6%)	3 (3.0%)	0	32 (3.4%)
Lumbar vertebral fracture	0	9 (1.1%)	2 (2.0%)	0	11 (1.2%)
Spinal compression fracture	1 (0.3%)	8 (1.0%)	0	0	8 (0.8%)
Foot fracture	0	5 (0.6%)	1 (1.0%)	0	6 (0.6%)
Spinal fracture	1 (0.3%)	6 (0.7%)	0	0	6 (0.6%)
Hip fracture	0	5 (0.6%)	0	0	5 (0.5%)
Humerus fracture	0	5 (0.6%)	0	0	5 (0.5%)
Thoracic vertebral fracture	0	4 (0.5%)	1 (1.0%)	0	5 (0.5%)
Upper limb fracture	1 (0.3%)	4 (0.5%)	1 (1.0%)	0	5 (0.5%)
Compression fracture	0	2 (0.2%)	2 (2.0%)	0	4 (0.4%)
Hand fracture	0	3 (0.4%)	1 (1.0%)	0	4 (0.4%)
Femur fracture	1 (0.3%)	3 (0.4%)	0	0	3 (0.3%)
Fractured sacrum	0	3 (0.4%)	0	0	3 (0.3%)
Pubis fracture	1 (0.3%)	3 (0.4%)	0	0	3 (0.3%)
Wrist fracture	0	2 (0.2%)	1 (1.0%)	0	3 (0.3%)
Acetabulum fracture	0	2 (0.2%)	0	0	2 (0.2%)
Ankle fracture	0	2 (0.2%)	0	0	2 (0.2%)

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Costal cartilage fracture	1 (0.3%)	2 (0.2%)	0	0	2 (0.2%)
Facial bones fracture	3 (0.8%)	2 (0.2%)	0	0	2 (0.2%)
Lower limb fracture	0	2 (0.2%)	0	0	2 (0.2%)
Osteoporotic fracture	2 (0.5%)	2 (0.2%)	0	0	2 (0.2%)
Pelvic fracture	0	1 (0.1%)	1 (1.0%)	0	2 (0.2%)
Sternal fracture	1 (0.3%)	1 (0.1%)	1 (1.0%)	0	2 (0.2%)
Avulsion fracture	1 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Fibula fracture	0	1 (0.1%)	0	0	1 (0.1%)
Fractured coccyx	0	1 (0.1%)	0	0	1 (0.1%)
Radius fracture	0	1 (0.1%)	0	0	1 (0.1%)
Stress fracture	0	1 (0.1%)	0	0	1 (0.1%)
Traumatic fracture	0	1 (0.1%)	0	0	1 (0.1%)
Cervical vertebral fracture	1 (0.3%)	0	0	0	0
Femoral neck fracture	1 (0.3%)	0	0	0	0
Tibia fracture	1 (0.3%)	0	0	0	0
Hypothyroidism	8 (2.0%)	65 (8.1%)	22 (22.0%)	0	87 (9.2%)
Hypothyroidism	5 (1.3%)	49 (6.1%)	15 (15.0%)	0	64 (6.8%)
Blood thyroid stimulating hormone increased	2 (0.5%)	20 (2.5%)	8 (8.0%)	0	28 (3.0%)
Thyroxine decreased	1 (0.3%)	4 (0.5%)	0	0	4 (0.4%)
Autoimmune thyroiditis	0	1 (0.1%)	0	0	1 (0.1%)
Thyroxine free decreased	0	1 (0.1%)	0	0	1 (0.1%)
Tri-iodothyronine decreased	0	1 (0.1%)	0	0	1 (0.1%)
Seizure	0	2 (0.2%)	0	0	2 (0.2%)
Seizure	0	2 (0.2%)	0	0	2 (0.2%)

Key: TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 19.1.

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- Skin rash

Most events were of Grade 1 or 2. Grade 3 events were reported for 5.2% of apalutamide-treated patients and 0.3% of placebo-treated patients. There were no reported events of toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) in the safety population.

Table 42. Number of subjects with treatment-emergent skin rashes by toxicity grade: safety population (Study ARN-509-003)

	Placebo					Apalutamide				
	Total	1	2	3	4	Total	1	2	3	4
Safety Population	398					803				
Subjects with worst grade skin rash	22	13	8	1	-	191	69	80	42	-
Subjects with first skin rash	22	16	6	-	-	191	91	69	31	-
Median time (days) to onset of first skin rash*	83.5	73.5	177.5	-	-	82.0	102.0	91.0	51.0	-
Resolved**	18 (81.8%)	12 (92.3%)	6 (75.0%)	0	-	154 (80.6%)	57 (82.6%)	63 (78.8%)	34 (81.0%)	-
Median time (days) to resolution	43.0	42.0	50.0	-	-	59.5	36.0	77.0	60.5	-
Received topical steroid	5 (22.7%)	2 (15.4%)	2 (25.0%)	1 (100.0%)	-	65 (34.0%)	15 (21.7%)	32 (40.0%)	18 (42.9%)	-
Received systemic steroid	4 (18.2%)	1 (7.7%)	2 (25.0%)	1 (100.0%)	-	33 (17.3%)	4 (5.8%)	12 (15.0%)	17 (40.5%)	-
Received antihistamine	4 (18.2%)	1 (7.7%)	2 (25.0%)	1 (100.0%)	-	67 (35.1%)	11 (15.9%)	28 (35.0%)	28 (66.7%)	-
Dose reduction	1 (4.5%)	1 (7.7%)	0	0	-	22 (11.5%)	0	11 (13.8%)	11 (26.2%)	-
Recurred after dose reduction	1 (4.5%)	1 (7.7%)	0	0	-	16 (8.4%)	0	7 (8.8%)	9 (21.4%)	-
Dose interruption	5 (22.7%)	3 (23.1%)	1 (12.5%)	1 (100.0%)	-	53 (27.7%)	4 (5.8%)	23 (28.8%)	26 (61.9%)	-
Recurred after dose interruption	0	0	0	0	-	29 (15.2%)	1 (1.4%)	14 (17.5%)	14 (33.3%)	-
Drug withdrawn	0	0	0	0	-	17 (8.9%)	0	3 (3.8%)	14 (33.3%)	-

* regardless of grade of first skin rash. The starting time for median calculation is the date of the first dose of the study drug.
** meaning all skin rashes were reported as resolved (regardless of initial or worst grade). The starting time for median calculation is the start date of the first skin rash.
Key: TEAE=treatment-emergent adverse event.
Note: Percent is based on the number of subjects in the 2nd row, by worst grade.
Note: Table does not include Grade 5 events.
Note: Treatment-emergent skin rashes are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity grade is used. If a subject has all skin rashes with missing toxicity grades, the subject is only counted in the total column.
Note: Skin rashes are coded using Medical Dictionary for Regulatory Activities Version 19.1.
Note: Toxicity Grade is based on NCI common toxicity criteria, version 4.0.

- Fall

Most falls were Grade 1-2. Falls that require hospitalization (Grade 3) were reported for 14 subjects (1.7%) in the apalutamide arm and 3 subjects (0.8%) in the placebo arm. Events of fall led to drug interruption for 3 apalutamide-treated subjects (0.4%) and for 0 placebo-treated subjects. No event of fall led to dose reduction. One subject (0.1%) in the ARN-509-003 apalutamide arm had an event of fall which led to discontinuation of study drug.

- Fracture

Exposure-standardized rates (events of fracture per 100 P-Y) for Study ARN-509-003 were 10.5 in the apalutamide arm and 7.8 in the placebo arm. For the combined apalutamide group, the exposure-standardized rate (events of fracture per 100 P-Y) was 9.9.

Most events of fracture were Grade 1 or 2. A Grade 3 event of fracture was reported for 22 apalutamide-treated subjects (2.7%) and 3 placebo-treated subjects (0.8%) in Study ARN-509-003. No Grade 4 event of fracture was reported in any of the 3 studies. Events of fracture led to drug interruption for 6 apalutamide-treated subjects (0.7%) and for 3 placebo-treated subjects (0.8%) in Study ARN-509-003, and for 8 subjects (0.8%) in the combined apalutamide group (the 2 additional subjects were from Study ARN-509-001).

No event of fracture led to dose reduction. One subject (0.1%) in the ARN-509-003 apalutamide arm had an event of fracture (rib) which led to discontinuation of study drug.

Fractures were often preceded by fall. Subjects who had an event of fracture reported a fall within 0-7 days prior in the apalutamide (40%) and placebo (50%) arms

- Seizure

Two subjects had an event of seizure, both in the apalutamide arm of Study ARN-509-003. One of the events (Grade 2) was considered by the investigator to be related to the study drug. The other event (Grade 1) was considered to be secondary to Grade 3 fall. Both events of seizure were reported as SAEs. Neither event of seizure had an outcome of death. As mandated by the study protocol, both events of seizure led to discontinuation of study drug.

- Hypothyroidism

Elevation of TSH generally occurred early during treatment, with the median time to first increased TSH being 113 days. Exposure-standardized rates (events per 100 P-Y) were 7.6 in the apalutamide arm and 2.2 in the placebo arm.

Only Grade 1 and 2 events of hypothyroidism were reported; no Grade 3 or 4 events of hypothyroidism were reported in any of the 3 studies. No event of hypothyroidism led to drug interruption. Events of hypothyroidism led to dose reduction for 1 apalutamide-treated subject (0.1%) in Study ARN-509-003. One subject (0.1%) in the ARN-509-003 apalutamide arm had an event of hypothyroidism which led to discontinuation of study drug.

AEs associated with hypothyroidism were reported more frequently among those subjects who were receiving thyroid replacement therapy at study entry. At study entry, 3.1% of subjects in the apalutamide arm and 4.3% of subjects in the placebo arm were receiving thyroid replacement therapy with levothyroxine. Fifty-eight of 778 subjects (7.5%) in the apalutamide arm who were not on thyroid replacement therapy at study entry had a hypothyroidism AE on study, compared to 7 of 25 subjects (28%) who were on thyroid replacement therapy at study entry. As TSH is monitored at regular intervals for all subjects on study treatment, and given the prevalence of hypothyroidism in the elderly population, 7 of 381 subjects (1.8%) in the placebo arm who were not on thyroid replacement therapy at study entry, compared to 1 of 17 subjects (5.9%) who were on thyroid replacement therapy at study entry, also had a hypothyroidism AE. Replacement therapy was started in 5.7% of apalutamide-treated patients during the study period (0.8% placebo), and an increased dose was required for 14 subjects (56%) of those already receiving such therapy at study entry (2 subjects [12%] in the placebo group).

Serious adverse event / deaths / other significant events

Table 43. Number of Subjects with Treatment-emergent Serious Adverse Events with Frequency of at Least 1% in Combined Apalutamide Group by System Organ Class and Preferred Term; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Subjects with 1 or more Serious TEAEs	93 (23.4%)	204 (25.4%)	32 (32.0%)	5 (11.1%)	241 (25.4%)
System organ class Preferred term					
Infections and infestations	9 (2.3%)	48 (6.0%)	2 (2.0%)	0	50 (5.3%)
Urinary tract infection	3 (0.8%)	10 (1.2%)	1 (1.0%)	0	11 (1.2%)
Renal and urinary disorders	38 (9.5%)	40 (5.0%)	3 (3.0%)	0	43 (4.5%)
Haematuria	8 (2.0%)	13 (1.6%)	2 (2.0%)	0	15 (1.6%)
Urinary retention	15 (3.8%)	10 (1.2%)	3 (3.0%)	0	13 (1.4%)

Key: TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 19.1.

Table 44. Number of Subjects with Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Integrated Safety

	ARN-509-003		ARN-509-001	56021927PCR1019	Combined
	Placebo	Apalutamide	Apalutamide	Apalutamide	Apalutamide
Analysis set: Integrated safety	398	803	100	45	948
Subjects with 1 or more TEAEs leading to death	1 (0.3%)	10 (1.2%)	1 (1.0%)	0	11 (1.2%)
System organ class Preferred term					
Cardiac disorders	1 (0.3%)	3 (0.4%)	0	0	3 (0.3%)
Acute myocardial infarction	0	1 (0.1%)	0	0	1 (0.1%)
Cardio-respiratory arrest	1 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Myocardial infarction	0	1 (0.1%)	0	0	1 (0.1%)
Infections and infestations	0	3 (0.4%)	0	0	3 (0.3%)
Sepsis	0	2 (0.2%)	0	0	2 (0.2%)
Pneumonia	0	1 (0.1%)	0	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.2%)	0	0	2 (0.2%)
Prostate cancer	0	2 (0.2%)	0	0	2 (0.2%)
General disorders and administration site conditions	0	1 (0.1%)	0	0	1 (0.1%)
Multiple organ dysfunction syndrome	0	1 (0.1%)	0	0	1 (0.1%)
Metabolism and nutrition disorders	0	0	1 (1.0%)	0	1 (0.1%)
Dehydration	0	0	1 (1.0%)	0	1 (0.1%)
Nervous system disorders	0	1 (0.1%)	0	0	1 (0.1%)
Cerebral haemorrhage	0	1 (0.1%)	0	0	1 (0.1%)
Psychiatric disorders	0	0	1 (1.0%)	0	1 (0.1%)
Confusional state	0	0	1 (1.0%)	0	1 (0.1%)

Key: TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 19.1.

Laboratory findings

Table 45. Summary of chemistry and hematology worst NCI toxicity grade during treatment: safety population

	Placebo						Apalutamide					
		NCI Toxicity Grade						NCI Toxicity Grade				
	Total N	0	1	2	3	4	Total N	0	1	2	3	4
Safety Population	398						803					
Chemistry												
Alkaline phosphatase increased	394	339 (86.0%)	51 (12.9%)	3 (0.8%)	1 (0.3%)	0	798	711 (89.1%)	84 (10.5%)	2 (0.3%)	1 (0.1%)	0
Alanine aminotransferase increased	394	318 (80.7%)	71 (18.0%)	5 (1.3%)	0	0	798	723 (90.6%)	69 (8.6%)	3 (0.4%)	3 (0.4%)	0
Aspartate aminotransferase increased	394	336 (85.3%)	54 (13.7%)	4 (1.0%)	0	0	798	663 (83.1%)	125 (15.7%)	7 (0.9%)	3 (0.4%)	0
Blood bilirubin increased	394	371 (94.2%)	20 (5.1%)	2 (0.5%)	1 (0.3%)	0	798	794 (99.5%)	3 (0.4%)	0	1 (0.1%)	0
Hypocalcemia (corrected)	365	244 (66.8%)	110 (30.1%)	10 (2.7%)	1 (0.3%)	0	778	521 (67.0%)	228 (29.3%)	23 (3.0%)	6 (0.8%)	0
Hypercalcemia (corrected)	365	358 (98.1%)	7 (1.9%)	0	0	0	778	749 (96.3%)	28 (3.6%)	0	1 (0.1%)	0
Cholesterol high	383	206 (53.8%)	167 (43.6%)	10 (2.6%)	0	0	766	182 (23.8%)	511 (66.7%)	72 (9.4%)	1 (0.1%)	0
Creatinine increased	394	285 (72.3%)	83 (21.1%)	22 (5.6%)	4 (1.0%)	0	798	568 (71.2%)	179 (22.4%)	47 (5.9%)	3 (0.4%)	1 (0.1%)
Hypokalemia	394	376 (95.4%)	0	17 (4.3%)	1 (0.3%)	0	797	786 (98.6%)	0	11 (1.4%)	0	0
Hyperkalemia	394	306 (77.7%)	62 (15.7%)	24 (6.1%)	2 (0.5%)	0	797	544 (68.3%)	179 (22.5%)	59 (7.4%)	15 (1.9%)	0
Hypomagnesemia	394	380 (96.4%)	13 (3.3%)	1 (0.3%)	0	0	798	772 (96.7%)	24 (3.0%)	2 (0.3%)	0	0
Hypermagnesemia	394	376 (95.4%)	18 (4.6%)	0	0	0	798	757 (94.9%)	39 (4.9%)	0	2 (0.3%)	0
Hypoalbuminemia	394	389 (98.7%)	4 (1.0%)	1 (0.3%)	0	0	798	757 (94.9%)	37 (4.6%)	4 (0.5%)	0	0
Hypoglycemia	391	382 (97.7%)	5 (1.3%)	2 (0.5%)	2 (0.5%)	0	797	774 (97.1%)	6 (0.8%)	13 (1.6%)	3 (0.4%)	1 (0.1%)
Hyperglycemia	391	159 (40.7%)	201 (51.4%)	27 (6.9%)	4 (1.0%)	0	797	237 (29.7%)	482 (60.5%)	59 (7.4%)	19 (2.4%)	0
Hyperuricemia	69	67 (97.1%)	1 (1.4%)	0	0	1 (1.4%)	132	124 (93.9%)	8 (6.1%)	0	0	0
Hyponatremia	394	359 (91.1%)	33 (8.4%)	0	2 (0.5%)	0	798	713 (89.3%)	76 (9.5%)	0	9 (1.1%)	0
Hypernatremia	394	305 (77.4%)	88 (22.3%)	1 (0.3%)	0	0	798	614 (76.9%)	177 (22.2%)	5 (0.6%)	2 (0.3%)	0
Hypertriglyceridemia	383	197 (51.4%)	151 (39.4%)	32 (8.4%)	2 (0.5%)	1 (0.3%)	766	251 (32.8%)	418 (54.6%)	85 (11.1%)	12 (1.6%)	0
Hematology												
Anemia	394	144 (36.5%)	231 (58.6%)	17 (4.3%)	2 (0.5%)	0	796	236 (29.6%)	512 (64.3%)	45 (5.7%)	3 (0.4%)	0
Hemoglobin increased	394	389 (98.7%)	4 (1.0%)	1 (0.3%)	0	0	796	790 (99.2%)	5 (0.6%)	0	1 (0.1%)	0
Lymphocyte count decreased	394	313 (79.4%)	34 (8.6%)	40 (10.2%)	7 (1.8%)	0	795	466 (58.6%)	171 (21.5%)	145 (18.2%)	13 (1.6%)	0
Lymphocyte count increased	394	394 (100.0%)	0	0	0	0	795	792 (99.6%)	0	3 (0.4%)	0	0
Neutrophil count decreased	394	361 (91.6%)	23 (5.8%)	9 (2.3%)	1 (0.3%)	0	795	678 (85.3%)	70 (8.8%)	41 (5.2%)	5 (0.6%)	1 (0.1%)
Platelet count decreased	394	368 (93.4%)	24 (6.1%)	1 (0.3%)	0	1 (0.3%)	796	733 (92.1%)	61 (7.7%)	1 (0.1%)	1 (0.1%)	0
White blood cell decreased	394	281 (71.3%)	105 (26.6%)	8 (2.0%)	0	0	796	424 (53.3%)	330 (41.5%)	40 (5.0%)	2 (0.3%)	0
Leukocytosis	394	394 (100.0%)	0	0	0	0	796	796 (100.0%)	0	0	0	0

Note: NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events.

Safety in special populations

Renal impairment

The PK of apalutamide in subjects with mild or moderate renal impairment was evaluated using a population PK approach, and had no discernible impact on the PK parameters. Consequently, dose adjustment in patients with mild or moderate renal impairment is not warranted.

Hepatic impairment

Results from the hepatic impairment study (Study 56021927PCR1018) showed that exposures to

Apalutamide were not meaningfully affected by mild or moderate hepatic impairment (Child-Pugh Class A or B). Hence, no dosage adjustment was deemed necessary for subjects with mild or moderate hepatic impairment. No data are available for subjects with severe hepatic impairment (Child-Pugh Class C).

Table 46. Overall Summary of Treatment-emergent Adverse Events by Hepatic Impairment Subgroups; Safety Population (Study ARN-509-003)

	Placebo		Apalutamide	
	Normal	Mild/Moderate	Normal	Mild/Moderate
Safety Population	363	35	723	80
Number of subjects with TEAEs	337 (92.8%)	34 (97.1%)	695 (96.1%)	80 (100.0%)
Drug-related[a]	194 (53.4%)	22 (62.9%)	510 (70.5%)	55 (68.8%)
Number of subjects with grade 3-4 TEAEs	121 (33.3%)	15 (42.9%)	324 (44.8%)	38 (47.5%)
Drug-related [a]	14 (3.9%)	3 (8.6%)	101 (14.0%)	12 (15.0%)
Number of subjects with treatment-emergent SAEs [b]	83 (22.9%)	9 (25.7%)	176 (24.3%)	23 (28.8%)
Drug-related[a]	6 (1.7%)	0	27 (3.7%)	4 (5.0%)
Grade 3-4	72 (19.8%)	4 (11.4%)	133 (18.4%)	17 (21.3%)
Number of subjects with TEAEs leading to treatment discontinuation	28 (7.7%)	0	80 (11.1%)	5 (6.3%)
Drug-related[a]	8 (2.2%)	0	55 (7.6%)	3 (3.8%)
Number of subjects with TEAEs leading to death	1 (0.3%)	0	9 (1.2%)	1 (1.3%)
Drug-related[a]	0	0	1 (0.1%)	0
All deaths within 28 days of last dose	1 (0.3%)	0	9 (1.2%)	1 (1.3%)
Adverse event	1 (0.3%)	0	6 (0.8%)	1 (1.3%)
Death due to prostate cancer	0	0	3 (0.4%)	0
Other	0	0	0	0

Key: TEAE=treatment-emergent adverse event; SAE=serious adverse event.
[a] Adverse events reported as related.
[b] Excludes Grade 5.
Note: Percent is based on the Safety population.
Note: Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days. For each category, subjects are counted only once, even if they experienced multiple events in that category.
Note: Hepatic impairment was categorized into normal, mild, moderate and severe categories per criteria, mild and moderate were pooled into one category due to small number of moderate, and no subject met severe criteria in this study.

[TSFAE01_HEP.RTF] [JNJ-56021927\ARN-509-003\DBR_IA\RE_ADHOC\PROD\TSFAE01_HEP.SAS] 15JUN2018, 00:00

Adverse events by age

In the combined apalutamide group and in the ARN-509-003 placebo arm, the safety profile observed in elderly subjects was generally consistent with that observed in younger subjects.

Table 47. Overall safety profile by age: integrated safety

	ARN-509-003									
	Placebo					Apalutamide				
		Age					Age			
	Total	<65	65-74	75-84	>=85	Total	<65	65-74	75-84	>=85
Analysis set: Integrated safety	398	43	168	150	37	803	106	306	328	63
Subjects with 1 or more:										
TEAEs	371 (93.2%)	39 (90.7%)	157 (93.5%)	141 (94.0%)	34 (91.9%)	775 (96.5%)	103 (97.2%)	290 (94.8%)	319 (97.3%)	63 (100.0%)
Related TEAEs[a]	216 (54.3%)	27 (62.8%)	89 (53.0%)	82 (54.7%)	18 (48.6%)	565 (70.4%)	76 (71.7%)	205 (67.0%)	233 (71.0%)	51 (81.0%)
Grade 3-4 TEAEs	136 (34.2%)	12 (27.9%)	54 (32.1%)	59 (39.3%)	11 (29.7%)	362 (45.1%)	39 (36.8%)	126 (41.2%)	166 (50.6%)	31 (49.2%)
Related TEAEs[a]	17 (4.3%)	1 (2.3%)	9 (5.4%)	6 (4.0%)	1 (2.7%)	113 (14.1%)	9 (8.5%)	26 (8.5%)	63 (19.2%)	15 (23.8%)
Serious TEAEs[b]	92 (23.1%)	8 (18.6%)	30 (17.9%)	42 (28.0%)	12 (32.4%)	199 (24.8%)	20 (18.9%)	69 (22.5%)	91 (27.7%)	19 (30.2%)
Related serious TEAEs[a]	6 (1.5%)	0	1 (0.6%)	5 (3.3%)	0	31 (3.9%)	0	8 (2.6%)	18 (5.5%)	5 (7.9%)
Grade 3-4 serious TEAEs	76 (19.1%)	6 (14.0%)	27 (16.1%)	34 (22.7%)	9 (24.3%)	150 (18.7%)	15 (14.2%)	49 (16.0%)	71 (21.6%)	15 (23.8%)
TEAEs leading to treatment discontinuation	28 (7.0%)	2 (4.7%)	8 (4.8%)	12 (8.0%)	6 (16.2%)	85 (10.6%)	3 (2.8%)	23 (7.5%)	44 (13.4%)	15 (23.8%)
Related TEAEs[a]	8 (2.0%)	1 (2.3%)	2 (1.2%)	4 (2.7%)	1 (2.7%)	58 (7.2%)	1 (0.9%)	18 (5.9%)	26 (7.9%)	13 (20.6%)
TEAEs leading to death	1 (0.3%)	0	0	0	1 (2.7%)	10 (1.2%)	0	0	8 (2.4%)	2 (3.2%)
Related TEAEs[a]	0	0	0	0	0	1 (0.1%)	0	0	0	1 (1.6%)
All deaths on treatment[c]	1 (0.3%)	0	0	0	1 (2.7%)	10 (1.2%)	0	0	8 (2.4%)	2 (3.2%)
Adverse event	1 (0.3%)	0	0	0	1 (2.7%)	7 (0.9%)	0	0	5 (1.5%)	2 (3.2%)
Death due to prostate cancer	0	0	0	0	0	3 (0.4%)	0	0	3 (0.9%)	0
Other	0	0	0	0	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019 are considered as on treatment death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. For each category, subjects are counted only once, even if they experienced multiple events in that category.

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Table 48. Overall safety profile by age: integrated safety

	ARN-509-001					56021927PCR1019				
	Apalutamide					Apalutamide				
		Age					Age			
	Total	<65	65-74	75-84	>=85	Total	<65	65-74	75-84	>=85
Analysis set: Integrated safety	100	23	43	24	10	45	16	23	5	1
Subjects with 1 or more:										
TEAEs	100 (100.0%)	23 (100.0%)	43 (100.0%)	24 (100.0%)	10 (100.0%)	37 (82.2%)	11 (68.8%)	20 (87.0%)	5 (100.0%)	1 (100.0%)
Related TEAEs[a]	88 (88.0%)	19 (82.6%)	38 (88.4%)	22 (91.7%)	9 (90.0%)	23 (51.1%)	5 (31.3%)	13 (56.5%)	4 (80.0%)	1 (100.0%)
Grade 3-4 TEAEs	47 (47.0%)	11 (47.8%)	17 (39.5%)	15 (62.5%)	4 (40.0%)	10 (22.2%)	3 (18.8%)	5 (21.7%)	1 (20.0%)	1 (100.0%)
Related TEAEs[a]	9 (9.0%)	1 (4.3%)	4 (9.3%)	4 (16.7%)	0	3 (6.7%)	0	2 (8.7%)	0	1 (100.0%)
Serious TEAEs[b]	32 (32.0%)	6 (26.1%)	11 (25.6%)	10 (41.7%)	5 (50.0%)	5 (11.1%)	2 (12.5%)	3 (13.0%)	0	0
Related serious TEAEs[a]	0	0	0	0	0	0	0	0	0	0
Grade 3-4 serious TEAEs	25 (25.0%)	4 (17.4%)	10 (23.3%)	8 (33.3%)	3 (30.0%)	5 (11.1%)	2 (12.5%)	3 (13.0%)	0	0
TEAEs leading to treatment discontinuation	16 (16.0%)	4 (17.4%)	7 (16.3%)	4 (16.7%)	1 (10.0%)	0	0	0	0	0
Related TEAEs[a]	6 (6.0%)	1 (4.3%)	2 (4.7%)	3 (12.5%)	0	0	0	0	0	0
TEAEs leading to death	1 (1.0%)	0	1 (2.3%)	0	0	0	0	0	0	0
Related TEAEs[a]	0	0	0	0	0	0	0	0	0	0
All deaths on treatment[c]	1 (1.0%)	0	1 (2.3%)	0	0	0	0	0	0	0
Adverse event	0	0	0	0	0	0	0	0	0	0
Death due to prostate cancer	1 (1.0%)	0	1 (2.3%)	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019 are considered as on treatment death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. For each category, subjects are counted only once, even if they experienced multiple events in that category.

[TSFAE01APART2OF3.RTF] [JNJ-56021927\Z_SCS\DBR_ARN509003SCS\RE_ARN509003SCS\PROD\TSFAE01A.SAS] 30AUG2017, 21:11

Table 49. Overall safety profile by age: integrated safety

	Combined Apalutamide				
		Age			
	Total	<65	65-74	75-84	>=85
Analysis set: Integrated safety	948	145	372	357	74
Subjects with 1 or more:					
TEAEs	912 (96.2%)	137 (94.5%)	353 (94.9%)	348 (97.5%)	74 (100.0%)
Related TEAEs[a]	676 (71.3%)	100 (69.0%)	256 (68.8%)	259 (72.5%)	61 (82.4%)
Grade 3-4 TEAEs	419 (44.2%)	53 (36.6%)	148 (39.8%)	182 (51.0%)	36 (48.6%)
Related TEAEs[a]	125 (13.2%)	10 (6.9%)	32 (8.6%)	67 (18.8%)	16 (21.6%)
Serious TEAEs[b]	236 (24.9%)	28 (19.3%)	83 (22.3%)	101 (28.3%)	24 (32.4%)
Related serious TEAEs[a]	31 (3.3%)	0	8 (2.2%)	18 (5.0%)	5 (6.8%)
Grade 3-4 serious TEAEs	180 (19.0%)	21 (14.5%)	62 (16.7%)	79 (22.1%)	18 (24.3%)
TEAEs leading to treatment discontinuation	101 (10.7%)	7 (4.8%)	30 (8.1%)	48 (13.4%)	16 (21.6%)
Related TEAEs[a]	64 (6.8%)	2 (1.4%)	20 (5.4%)	29 (8.1%)	13 (17.6%)
TEAEs leading to death	11 (1.2%)	0	1 (0.3%)	8 (2.2%)	2 (2.7%)
Related TEAEs[a]	1 (0.1%)	0	0	0	1 (1.4%)
All deaths on treatment[c]	11 (1.2%)	0	1 (0.3%)	8 (2.2%)	2 (2.7%)
Adverse event	7 (0.7%)	0	0	5 (1.4%)	2 (2.7%)
Death due to prostate cancer	4 (0.4%)	0	1 (0.3%)	3 (0.8%)	0
Other	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019 are considered as on treatment death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. For each category, subjects are counted only once, even if they experienced multiple events in that category.

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Adverse events by race

Table 50. Overall safety profile by race: integrated safety

	ARN-509-003									
	Placebo					Apalutamide				
		Race					Race			
	Total	White	Black	Asian	Other	Total	White	Black	Asian	Other
Analysis set: Integrated safety	341	273	20	47	1	668	522	48	92	6
Subjects with 1 or more:										
TEAEs	315 (92.4%)	254 (93.0%)	18 (90.0%)	42 (89.4%)	1 (100.0%)	643 (96.3%)	503 (96.4%)	47 (97.9%)	87 (94.6%)	6 (100.0%)
Related TEAEs[a]	185 (54.3%)	160 (58.6%)	10 (50.0%)	14 (29.8%)	1 (100.0%)	469 (70.2%)	376 (72.0%)	31 (64.6%)	58 (63.0%)	4 (66.7%)
Grade 3-4 TEAEs	115 (33.7%)	96 (35.2%)	6 (30.0%)	12 (25.5%)	1 (100.0%)	309 (46.3%)	246 (47.1%)	25 (52.1%)	35 (38.0%)	3 (50.0%)
Related TEAEs[a]	15 (4.4%)	12 (4.4%)	1 (5.0%)	1 (2.1%)	1 (100.0%)	95 (14.2%)	67 (12.8%)	10 (20.8%)	17 (18.5%)	1 (16.7%)
Serious TEAEs[b]	76 (22.3%)	63 (23.1%)	1 (5.0%)	11 (23.4%)	1 (100.0%)	169 (25.3%)	133 (25.5%)	13 (27.1%)	23 (25.0%)	0
Related serious TEAEs[a]	6 (1.8%)	5 (1.8%)	0	1 (2.1%)	0	28 (4.2%)	18 (3.4%)	5 (10.4%)	5 (5.4%)	0
Grade 3-4 serious TEAEs	62 (18.2%)	51 (18.7%)	1 (5.0%)	9 (19.1%)	1 (100.0%)	127 (19.0%)	102 (19.5%)	9 (18.8%)	16 (17.4%)	0
TEAEs leading to treatment discontinuation	25 (7.3%)	18 (6.6%)	2 (10.0%)	5 (10.6%)	0	71 (10.6%)	48 (9.2%)	11 (22.9%)	12 (13.0%)	0
Related TEAEs[a]	7 (2.1%)	5 (1.8%)	1 (5.0%)	1 (2.1%)	0	48 (7.2%)	31 (5.9%)	8 (16.7%)	9 (9.8%)	0
TEAEs leading to death	1 (0.3%)	0	0	1 (2.1%)	0	7 (1.0%)	6 (1.1%)	1 (2.1%)	0	0
Related TEAEs[a]	0	0	0	0	0	0	0	0	0	0
All deaths on treatment[c]	1 (0.3%)	0	0	1 (2.1%)	0	7 (1.0%)	6 (1.1%)	1 (2.1%)	0	0
Adverse event	1 (0.3%)	0	0	1 (2.1%)	0	4 (0.6%)	3 (0.6%)	1 (2.1%)	0	0
Death due to prostate cancer	0	0	0	0	0	3 (0.4%)	3 (0.6%)	0	0	0
Other	0	0	0	0	0	0	0	0	0	0

Key: TEAE = treatment-emergent adverse event
[a]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]Grade 5 events are not included.
[c]Deaths within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019 are considered as on treatment death.
Note: Treatment-emergent adverse events are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for study 56021927PCR1019. For each category, subjects are counted only once, even if they experienced multiple events in that category.

Adverse events by baseline ECOG performance status

Of the 948 subjects in the combined apalutamide group, 721 subjects (76%) had an ECOG score

of 0 and 227 subjects (24%) had an ECOG score of 1. The rates of Grade 3-4 AEs (ECOG 1:

51%; ECOG 0: 42%), SAEs (ECOG 1: 32%; ECOG 0: 23%), and AEs leading to treatment discontinuation (ECOG 1: 16%; ECOG 0: 8.9%) were higher in subjects with an ECOG score of

1 compared to subjects with an ECOG score of 0.

Adverse events by number of prior hormonal therapies

Of the 943 subjects in the combined apalutamide group for whom prior hormonal therapy information was available, 176 subjects (19%) received 1 prior hormonal therapy and 767 subjects (81%) received 2 or more prior hormonal therapies. In general, the overall rates of AEs, Grade 3-4 AEs, SAEs, and AEs leading to treatment discontinuation were similar for the 1 and ≥2 prior hormonal therapy groups.

Adverse events by baseline PSADT

Baseline PSADT was collected in Studies ARN-509-003 and ARN-509-001. Of the 847 subjects in the combined apalutamide group for whom a baseline PSADT value was available, 235 subjects (28%) had a PSADT >6 months and 612 subjects (72%) had a PSADT ≤6 months. In general, the overall rates of AEs, Grade 3-4 AEs,

SAEs, and AEs leading to treatment discontinuation were similar for the PSADT >6 months and PSADT ≤6 months groups.

Adverse events by bone-sparing agent use at baseline

In the combined apalutamide group, only 14% of subjects were using bone-sparing agents at baseline. The relationship between bone-sparing agent use prior to study entry and events in the grouped term of fracture is discussed in the AE of special interest section.

Extrinsic factors (AEs by geographic region)

In the combined apalutamide group, 42% subjects were from North America, 45% from Europe, and 13% from the Rest of the World. The overall rates of AEs, Grade 3-4 AEs, SAEs, and AEs leading to treatment discontinuation were similar for subjects from North America, Europe, and Rest of World. Subjects from Europe had lower rates of AEs overall and AEs leading to treatment discontinuation as compared with the other geographic region groups.

Discontinuation due to adverse events

Adverse events leading to treatment discontinuation

The percentage of subjects reported with TEAEs leading to treatment discontinuation was higher in the apalutamide arm (11%) compared with the placebo arm (7.0%), with TEAEs in the SOC of Skin and Subcutaneous Tissue Disorders resulting in the highest incidence of treatment discontinuations.

Skin rash was the most common reason for treatment discontinuation in Study ARN-509-003: 19 subjects (2.4%) in the apalutamide arm and 0 subjects in the placebo arm. Two subjects enrolled to Study ARN-509-001 discontinued apalutamide therapy due to events of skin rash.

Fatigue was the next most common TEAE leading to treatment discontinuation (1.0% apalutamide versus 0.3% placebo). All other TEAEs leading to treatment discontinuation occurred at a low percentage (<1%).

Adverse events leading to dose interruption, reduction, or other modifications

TEAES leading to dose reduction were reported for 9.6% of subjects in the apalutamide arm and 1.8% of subjects in the placebo arm. The most frequently reported TEAEs leading to dose reduction (reported for >1% of subjects in either arm) were skin rash as the grouped term (2.7% apalutamide versus 0.3% placebo) and fatigue (1.7% apalutamide versus 0% placebo).

TEAEs leading to dose interruption were reported for 30% of subjects in the apalutamide arm and 18% of subjects in the placebo arm. The most frequently reported TEAEs leading to interruption of treatment (reported for >1% of subjects in either arm) were skin rash as the grouped term (6.8% apalutamide vs.1.3% placebo), diarrhoea (2.4% apalutamide vs. 1.3% placebo),nausea (1.5% apalutamide vs. 1.0% placebo), vomiting (1.1% apalutamide vs. 1.0% placebo), fatigue (2.2% apalutamide vs. 0.5% placebo), urinary tract infection (0.5 apalutamide vs. 1.3% placebo), hematuria (1.1% apalutamide vs. 0.5% placebo), and hypertension (1.2% apalutamide vs. 0.8% placebo).

Post marketing experience

2.6.1. Discussion on clinical safety

The assessment of the safety profile of apalutamide in the proposed indication is based mainly on the results of the phase III study ARN-509-003, which encompassed 1,201 patients with NM-CRPC that were randomized to receive apalutamide plus androgen deprivation therapy (ADT) [n=803] or placebo plus ADT [n=398]. Additionally, data on other 145 patients from studies ARN-509-001 (n=100), a phase1/2 study and study 56021927PCR1019 (n=45), a phase 1b study, have been presented. Studies ARN-509-001 and 56021927PCR1019 included patients with both NM-CRPC and mCRPC. Apalutamide was administered at a dose of 240 mg once daily.

Exposure to apalutamide could be considered sufficient to the assessment of the safety profile. Median exposure to apalutamide was longer than to placebo (16.92 months [range: 0.1; 42.0] vs. 11.17 months [0.1; 37.1], respectively), with 70% and 26% of patients receiving apalutamide for ≥12 months and ≥24 months, respectively (45% and 11% with placebo). As of the data cut-off (19 May 2017), 61% of patients in the apalutamide arm and 30% of placebo-treated patients were still on treatment. Treatment compliance of at least 95% was reported for approximately 48% of patients in the apalutamide arm compared to 67% of patients in the placebo arm.

Overall treatment discontinuations were more common in the placebo arm compared to apalutamide arm (70.1% vs. 39.1%, respectively), mostly due to progressive disease (52.8% placebo vs. 19.3% apalutamide). Dose reductions (21% apalutamide vs. 15% placebo) and dose interruptions (77% apalutamide vs. 67% placebo) were more frequent with apalutamide. Differences were mainly driven by dose modifications related to AEs. Additionally, there were dose interruptions (43.1% apalutamide vs 47.2% placebo) and dose reductions (9.7% vs 11.3%) due to “other” reason. According to the applicant, the majority of them (approximately 99% and 75%, repectively) were due to the subject inadvertenly missing or forgotting to take 1 or more doses of apalutamide or placebo.

Common adverse events

Overall incidence of adverse events (AEs) was similar between treatment arms (96.5% apalutamide vs. 93.2% placebo). However, the proportion of treatment-related AEs was higher in the apalutamide arm (70.4% vs. 54.3%). The most commonly reported AEs that remained higher in the apalutamide arm when adjusted for exposure (events per 100 patients-year) were fatigue (32.3% vs. 27.2%), arthralgia (14.7% vs. 8.0%) and weight decreased (18.3% vs. 10.5%). Other less common AEs included rash (12.0% vs. 4.6%), pruritus (5.6% vs. 1.5%), hypercholesterolemia (4.6% vs. 1.7%) and hypertriglyceridemia (3.4% vs. 1.0%).

Proportion of hypertension was significantly higher in the pivotal trial (24.8%) compared to phase I and Ib trials (8% and 2.2%). The proportion of subjects with hypertension reported as a TEAE in the Phase 3 randomized, placebo-controlled trial was nearly similar in the apalutamide and placebo arms; therefore, the PT of hypertension is not attributable to apalutamide exposure in Study ARN-509-003. The Phase 1 and Phase 1b studies were conducted at a different time and enrolled a different subject population; thus, it is not possible to compare the frequency of reporting of the PT of hypertension.

Grade 3-4 AEs were more frequent with apalutamide than with placebo (45.1% vs. 34.2%). Grade 3-4 AEs occurring in ≥1% of apalutamide treated patients and with ≥0.5% higher incidence compared to placebo were hypertension (14.3% vs. 11.8%), pneumonia (1.1% vs. 0.8%), rash maculo-papular (1.9% vs. 0), rash (1.2% vs. 0.3%), syncope (2.1% vs. 1%), fall (1.7% vs. 0.8%), weight decreased (1.1% vs. 0.3%), hyperkalaemia

(1% vs. 0.3%), hyperglycemia (1% vs. 0.5%) and diarrhea (1% vs. 0.5%). When adjusted for exposure, rash, syncope, fall and weight decreased remained higher in the apalutamide arm. Treatment-related grade 3-4 AEs were also more common in patients treated with apalutamide than with placebo (14.07% vs. 4.3%, respectively). Hypertension (2.1% apalutamide vs. 2.0% placebo) and skin-related events (5.4% apalutamide vs. 0 placebo) were the most commonly reported grade 3 related TEAEs (≥1%). No grade 4 drug-related TEAEs with a ≥1% frequency were reported.

The applicant has provided an adequate statistical analysis of correlation between the time to discontinuation and timing and incidence of TEAEs. The applicant also submitted Kaplan-Meier plot for TEAES leading to treatment discontinuation and censored severe (grade 3-4) TEAES.

Serious adverse events (SAEs)

The proportion of patients that reported SAEs was similar between treatment arms (25.4% apalutamide vs. 23.4% placebo). Of these, 3.9% of patients in the apalutamide arm and 1.5% in the placebo arm reported SAEs that were considered by the investigator as related to study drug.

SAEs most commonly reported (≥1%) in the apalutamide arm with a higher incidence compared to placebo were urinary tract infection (1.2% vs. 0.8%), pneumonia (1.1% vs. 0.5%), sepsis (1.0% vs. 0) and fracture grouped term (3.4% vs. 0.8%).

Deaths

In study ARN-509-003 AEs leading to death occurred in 10 (1.2%) patients in the apalutamide arm (11 subjects in the combined apalutamide group). The majority of deaths were related to the SOC of cardiac disorders and infections and infestations (3 [0.4%], each). Only one of the deaths was considered by the investigator as related to study drug (a myocardial infarction in a patient who had prior history of myocardial infarction).

Adverse events of special interest (AEOSIs)

Adverse events considered of special interest with apalutamide include skin rash grouped term, fall, fracture, seizure and hypothyroidism.

Skin rash (grouped term): skin rash was the most commonly reported AEOSI, with a higher incidence in the apalutamide arm for all (23.8% vs. 5.5%) and grade 3-4 events (5.2% vs 0.3%). Most events (81%) resolved with commonly used medications (median time to resolution: 59.5 days vs. 43 days, respectively). No events of toxic epidermal necrolysis (TEN) or Steven-Johnson syndrome (SJS) were reported.

Fall: events of fall were reported with apalutamide in a higher rate than with placebo (16% vs. 9.0%, respectively) although when adjusted for treatment duration differences between treatment arms were reduced (13.6% vs. 10.0%). Fourteen (1.7%) patients in the apalutamide arm required hospitalization due to grade 3 AEs of fall.

Fracture: 94 (12%) patients in the apalutamide arm reported events of fracture compared to 26 (6.5%) patients in the placebo arm. The incidence of fracture appears to be related to treatment duration, being higher after one year of treatment. Grade 3 events were reported in 22 (2.7%) of patients in the apalutamide arm. Approximately 40% of events in the apalutamide arm were preceded by a previous fall. The mechanistic relationship between the increased risk of fall and fracture with the study drug is not completely understood. Further investigations to identify risk factors correlated with these adverse events and possible preventive measures are needed, especially in the context of long-term exposure to the drug.

Seizure: two (0.2%) events of seizure were reported, both during study ARN-509-003. One of the events was considered to be related to study drug while the other occurred in the context of a trauma after a fall. In both cases, apalutamide treatment was discontinued, as per protocol.

Regarding non clinical data, apalutamide has been associated with a potential for seizure, considering the inhibition of GABA A receptor as the mechanism for the seizure observed in non clinical studies. Convulsions have also been reported in clinical trials with enzalutamide, a potent androgen receptor signalling inhibitor.

Nevertheless, neurologic events could be underestimated since patients with predisposing conditions or concomitant medications that could lower the seizure threshold were excluded.

Hypothyroidism: In study ARN-509-003 hypothyroidism was reported in 65 (8.1%) patients in the apalutamide arm compared to 8 (2.0%) patients in the placebo arm. The incidence of hypothyroidism was higher in those patients who were receiving thyroid replacement therapy with levothyroxine at study entry (7/25 [28.0%] apalutamide vs. 1/17 [5.9%] placebo). Enzyme induction of UGT through induction for CYP3A4 is deemed to be the cause for this effect. Patients with an altered pituitary-thyroid axis, such as those with hypothirodism, would not be able to compensate alterations in thyroxine metabolism so adjustment of exogenous hormone administration may be required for those on thyroid replacement hormone.

Intrinsic factors

Regarding age, no differences were observed in the overall incidence of AEs between groups. However grade 3-4 AEs, SAEs and discontinuation due to AEs were more common in patients older than 75 years, mainly those AEs considered related to study drug.

The majority of patients included in study ARN-509-003 had normal hepatic function (723 [90%]). Only 2 patients had moderate hepatic impairment, thus safety data in this population are limited. However, according to a population PK approach and a pharmacokinetic single-dose study (n=24), exposure to apalutamide and its metabolite N-desmethyl apalutamide does not seem to be affected by mild or moderate hepatic impairment, therefore no major differences in the safety profile of apalutamide would be expected in patients with moderate hepatic impairment. Apalutamide has not been studied in patients with severe hepatic impairment.

The majority of patients included in the pivotal trial were white, while only 6.6% and 11% were black or Asian, respectively. Of note, grade 3-4 treatment-related AEs were more frequent in black (20.8%) and Asian (18.5%) patients compared to white patients (12.8%). Additionally, treatment-related SAEs and AEs related to study drug leading to discontinuation were also more commonly reported in black patients (10.4% and 16.7%, respectively) compared to Asian (5.4% and 9.8%) and white (3.4% and 5.9%) patients. Nevertheless, these differences canot be attributed to any PT in particular and taking into account the small sample size of the subgroup of Black patients (n=48) it is difficult to conclude that those differences could be related to apalutamide treatment.

Laboratory abnormalities

The most common hematologic laboratory abnormality observed in both treatment arms was anaemia (70.4% apalutamide vs. 63.5% placebo). The proportion of patients with lymphocyte count decreased was twice as high in patients treated with apalutamide compared to placebo (41.4% vs. 20.6%) as well as neutrophil count decreased (17.4% vs. 8.4%). Most cases were grade 1 or grade 2. The most frequently reported grade 3 hematologic laboratory abnormality was lymphocyte count decrease. Decreasing in lymphocyte and neutrophil count occurs during the first cycles of treatment and then remain stable.

Cholesterol high, hiperkalemia, hyperglycaemia and hypertriglyceridemia were more frequent in patients treated with apalutamide.

ECG evaluations from Study ARN-509-003 and the dedicated QT/QTc Study 56021927PCR1019 showed no significant effect of apalutamide on ventricular repolarisation. However, further clarifications were requested. After reviewing, risk of potential QT prolongation in patients with clinically significant cardiovascular disease cannot be fully ruled out. Thus, the feasibility to conduct a PASS to characterize the risks of use in the subgroup of population of patients with clinically significant cardiovascular disease should be discussed by the applicant (see RMP).

From the safety database all the adverse reactions reported in clinical trials have been reflected in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

Overall, apalutamide appears to be well tolerated. Fatigue (30.4%), hypertension (24.8%), skin rash (23.8%) and diarrhoea (20.3%) were the most commonly reported adverse events. Other adverse events of special interest associated to apalutamide treatment were fracture (12%), fall (15.6%), seizure (0.2%) and

hypothyroidism (8.1%). Skin rash as a grouped term was the main adverse event related to treatment discontinuations and dose modifications.

Since the new therapy is supposed to prevent metastases in patients without symptoms of the disease, an important issue is considered to be a good level of safety and tolerability of the drug.

A relatively high proportion of grade 3 TEAEs were reported with apalutamide compared to placebo. Given that OS data are still immature, the impact of apalutamide on OS compared to placebo remains uncertain. In this context, impact of apalutamide treatment on QoL plays a crucial role, moreover considering the intended long term use of apalutamide. However, QoL analyses do not appear to show a detrimental effect.

All in all, the safety profile of apalutamide is considered acceptable and sufficiently characterised.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Seizures Fall Non-pathological fracture
Important potential risks	None
Missing information	Use in patients with severe hepatic impairment Use in patients with clinically significant cardiovascular disease Carcinogenic potential

Pharmacovigilance plan

Trial Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Phase 1 PK study A single-dose, open-label study to evaluate the pharmacokinetics of apalutamide in subjects with severe hepatic impairment compared with subjects with normal hepatic function. Planned	To characterise the single dose PK and safety of apalutamide in subjects with impaired hepatic function relative to subjects with normal hepatic function.	Use in patients with severe hepatic impairment	Protocol submission Study start Final results Final report	September 2019 January 2020 31 March 2022 31 January 2023

Trial Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A feasibility assessment of a prospective, observational safety study to characterise the risks of the use of apalutamide in NM-CRPC patients on ADT with clinically significant cardiovascular conditions. Planned	To better characterise the risks of use of apalutamide in the subgroup of patients with clinically significant cardiovascular disease.	Use in patients with clinically significant cardiovascular disease	Feasibility assessment report Final results Final reports	31 March 2019 30 April 2023 31 August 2023
2-year carcinogenicity study in male rat Ongoing	To better characterise the carcinogenic potential of apalutamide	Carcinogenic potential	Final report	30 September 2021
6-month carcinogenicity study in the male transgenic Tg.rasH2 mice Planned	To better characterise the carcinogenic potential of apalutamide	Carcinogenic potential	Final report	30 September 2020

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Seizures	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.7 SmPC Section 4.8 PL Section 2 PL Section 4 Advice on the use of apalutamide in patients who develop a seizure is provided in SmPC Section 4.4 and PL Section 4 Advice on the use of apalutamide in patients with a history of seizures or other predisposing factors is provided in SmPC Section 4.4 Warning to the use of apalutamide with concomitant medicinal products that lower the seizure threshold is provided in SmPC Section 4.4 and PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TFUQ to obtain structured information on reported suspected adverse reaction of seizures Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Legal status Additional risk minimisation measures: None	
Fall	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Recommendation to evaluate patients for fall risk is provided in SmPC Section 4.4 and PL Section 4 A warning for patients to take extra care to reduce risk of fall is provided in PL Section 2 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TFUQ to obtain structured information on reported suspected adverse reaction of fall Additional pharmacovigilance activities: None
Non-pathological fracture	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Recommendation to evaluate patients for fractures risk, to monitor and manage patients at risk for fractures according to established treatment guidelines, and to consider use of bone targeted agents is provided in SmPC Section 4.4 and PL Section 4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TFUQ to obtain structured information on reported suspected adverse reaction of fractures Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 5.2 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Phase 1 PK study
Use in patients with clinically significant cardiovascular disease	Routine risk minimisation measures: SmPC Section 4.4 Recommendation to monitor patients with clinically significant cardiovascular disease for risk factors such as hypercholesterolaemia, hypertriglyceridaemia, or other cardio-metabolic disorders, and to treat, if appropriate, after initiating apalutamide for these conditions according to established treatment guidelines is provided in SmPC Section 4.4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TFUQ to obtain structured information on reported suspected adverse reaction of cardiovascular events Additional pharmacovigilance activities: A feasibility assessment of a prospective, observational safety study to characterise the risks of the use of apalutamide in NM-CRPC patients on ADT with clinically significant cardiovascular conditions
Carcinogenic potential	Routine risk minimisation measures: • Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Nonclinical study TOX11338 • Nonclinical study TOX13540

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14-02-18. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of apalutamide with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers apalutamide to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the immediate labelling has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The product will be marketed as film-coated tablets supplied in blisters sealed in a wallet card. The company requested to omit printing certain of the minimum particulars on the blister foil as patients will not be able to see it since it will be completely sealed in an inner wallet. The inner wallet will contain all the required minimum particulars for the primary packaging and will be translated in all languages.

The QRD Group agreed to print the minimum particulars on the blister foil as follows: invented name, INN, strength, EXP/Lot. The only particulars that would need translation on the blister foil are the INN, EXP and Lot, and the QRD Group agreed to have these particulars in English only.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on the EMA website, but the printed materials will only be in English as agreed by the QRD Group.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Erleada (apalutamide) is included in the additional monitoring list as new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Erleada is indicated for the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease (PSADT ≤10 months).

3.1.2. Available therapies and unmet medical need

At the time of this MAA, there were no approved treatments for patients with NM-CRPC. Patients with NM-CRPC are largely asymptomatic so the burden of long-term toxicities and the potential for negative impact on quality of life are major considerations in the selection of therapy. First-generation antiandrogens (bicalutamide, nilutamide, flutamide), ketoconazole, estrogens, and corticosteroids administered in combination with ADT have been used in the NM-CRPC setting, with no durability of response.

3.1.3. Main clinical studies

Efficacy data in support of this application focus on data from trial ARN-509-003 (SPARTAN): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Apalutamide compared with placebo in a total of 1207 subjects (2:1) with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer who had rapidly rising PSA (PSA doubling time ≤10 months).

3.2. Favourable effects

Results from SPARTAN trial in the efficacy target population of patients at the cut-off date of 19 May 2017 included the main analysis planned for MFS (BIRC assessed) and the first interim analysis for OS (2 IA planned plus 1 final analysis).

With an event rate of 25.9% and 52.4% for apalutamide and placebo arms respectively, a statistically significant improvement in MFS was observed in favour of apalutamide (HR: 0.297; 95% CI: 0.244, 0.362). The median MFS (95% CI) was 40.51 months (95% CI: NE, NE) in the apalutamide group and 15.70 months (95% CI: 14.55, NE) in the placebo group (Δ 24.81 months). These results are supported by several sensitivity analyses as well as by subgroups analyses.

Most secondary endpoints showed consistency with primary efficacy outcomes. Treatment with apalutamide delayed time to Time to metastasis (HR: 0.271; 95% CI: 0.219, 0.335) and PFS (HR:0.291; 95% CI: 0.238,0.356) however these endpoints are closely related to the primary endpoint by definition.

A statistically significant effect was demonstrated for time to symptomatic progression (HR: 0.447; 95%CI: 0.315, 0.634), however the number of events is limited (event rate of 7.9% in apalutamide arm and 15.7% in placebo arm).

OS data, still highly immature at the time of the first IA so as to draw any firm conclusion (event rate 7.7% and 10.5% in apalutamide and placebo arms respectively), did not cross the boundary for statistical significance (HR=0.700, 95% CI: 0.472, 1.038) and although an initial separation of the survival curves is observed, no firm conclusion can be drawn.

PFS2 data (as of the 17 May 2018), with 20.1% and 29.9% of events in apalutamide and placebo arms, showed an initial trend towards greater reduction of risk of disease progression with next line therapy or death for patients initially allocated to apalutamide arm compared to placebo (HR: 0.449, 95% CI: 0.393, 0.632).

Time to cytotoxic chemotherapy did not ether show a statistically significant effect, however a trend towards superiority is observed in favour of apalutamide (HR=0.435, 95% CI: 0.286, 0.661).

Patient-reported outcome results seem to indicate maintenance of overall health related quality of life with the addition of apalutamide to ADT in this population of generally asymptomatic NM-CRPC subjects. Similar mean changes from baseline or median time to worsening in the Functional Assessment of Cancer Therapy–Prostate (FACT-P) were observed in the 2 treatment arms. For nearly all time points, no differences between apalutamide and placebo were observed in change from baseline across the EQ visual analogue scale (VAS).

3.3. Uncertainties and limitations about favourable effects

The main uncertainty of the present application is related to the use of a new variable (MFS) in a setting where no treatment is established. Despite a clear statistically significant reduction in terms of MFS was demonstrated in the pivotal trial, in the absence of more mature OS data it seems difficult to conclude about the long term relevance of such finding.

Despite time to symptomatic progression showing a statistically significant effect, which could be relevant when it comes to assessing the benefit of apalutamide treatment, the data are relatively immature.

Updated efficacy results are expected (PAES).

3.4. Unfavourable effects

The safety profile of apalutamide in the proposed indication is based mainly on the results of the phase III study ARN-509-003 (which encompassed 1,201 patients with NM-CRPC thatOv were randomized to receive apalutamide plus androgen deprivation therapy (ADT) [n=803] or placebo plus ADT [n=398]) and data on other 145 patients from studies ARN-509-001 (a phase1/2 study; n=100) and study 56021927PCR1019 (a phase 1b study; n=45), in which apalutamide was administered at a dose of 240 mg once a day. Studies ARN-509-001 and 56021927PCR1019 included patients with both NM-CRPC and mCRPC.

Median exposure to apalutamide in study ARN-509-003 was 16.92 months [range: 0.1; 42.0] (compared to 11.17 months [range: 0.1; 37.1] with placebo), with 70% and 26% of patients receiving apalutamide for ≥12 months and ≥24 months, respectively (45% and 11% with placebo).

In the study ARN-509-003 the most commonly reported AEs (≥ 15%; by PT) were fatigue (30.4%), hypertension (24.8%), diarrhoea (20.3%), nausea (18.1%), weight decreased (16.1%), arthralgia (15.9%) and fall (15.6%).

Grade 3-4 AEs were reported in 45.1% of patients, with 14.07% being considered related to study drug by the investigator. The most frequent grade 3-4 AEs were hypertension (14.3%), syncope (2.1%), rash maculo-papular (1.9) and fall (1.7%).

SAEs were reported in 25.4% of patients (3.9% of them were considered by the investigator as related to study drug). SAEs most commonly reported (≥1%) in the apalutamide arm with a higher incidence compared to placebo were urinary tract infection (1.2%), pneumonia (1.1%), sepsis (1.0%) and fracture grouped term (3.4%).

In study ARN-509-003 AEs leading to death occurred in 10 (1.2%) patients in the apalutamide arm. The majority of deaths were related to the SOC of cardiac disorders and infections and infestations (3 [0.4%], each). Only one of the deaths was considered by the investigator as related to study drug (a myocardial infarction in a patient who had prior history of myocardial infarction).

Skin rash grouped term, seizure, fall, fracture and hypothyroidism are adverse events of special interest associated to apalutamide treatment, reported in 42% of subjects.

Skin rash was the most frequently reported apalutamide treatment related AE, although most of the events were Grade 1-2.

In the study ARN-509-003, 10.7% of patients discontinued treatment with apalutamide (compared to 6.3% with placebo) due to AEs. Additionally, dose reductions and dose interruptions due to AEs were required in 11.2% of patients (3.3% placebo) and 33.6% of patients (19.3% placebo). Skin rash was the main AEs related to discontinuations, dose reductions and dose interruptions.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile of apalutamide could be considered well characterised. There are no important uncertainties about unfavourable effects.

3.6. Effects Table

Table 1: Effects Table for apalutamide in high risk NM-CRPC (data cut-off: 19 May 2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
MFS	Primary	Median mo (95% CI)	40.51 (NE, NE)	15.70 (14.55, NE)	Main analysis with 25.9% of events in Apalut arm vs. 52.4% events in Pl arm. HR (95% CI): 0.297 (0.244,0.362)	Efficacy section
Time to metastasis	Secondary	Median mo (95% CI)	40.51 (NE, NE)	16.59 (14.59, 18.46)	21.7% of events in Apalut arm vs. 47.6% events in Pl arm.	
PFS	Secondary	Median mo (95% CI)	40.51 (NE, NE)	14.72 (14.49, 18.37)	24.8% of events in Apalut arm vs. 50.9% events in Pl arm.	
Time to Symptomatic Progression	Secondary	Median mo (95% CI)	NE (NE, NE)	NE (36.83, NE)	7.9% of events in Apalut arm vs. 15.7% events in Pl arm. HR (95% CI): 0.447 (0.315,0.634)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
OS	Secondary	mo (95% CI)	NE (NE, NE)	39.03 (39.03, NE)	1st IA with 7.7% of events in Apalut arm vs. 10.5% in Pl arm HR (95% CI): 0.700 (0.472,1.038)	
Time to initiation of cytotoxic chemotherapy	Secondary	mo (95% CI)	NE (NE, NE)	NE (NE, NE)	5.7% of events in Apalut arm vs. 11% events in Pl arm. Not crossed statistical significance boundary.	
Unfavourable Effects						
Grade 3-4 TEAEs	TEAEs grade 3-4 regardless causality	%	45.1	34.2		Safety section
Serious TEAEs	Serious TEAEs regardless causality	%	24.8	23.1		
Deaths	Number of deaths related to TEAEs regardless causality	n (%)	10 (1.2)	1 (0.3)		
Skin rash	AEOSI	%	23.8	5.5		
Seizure	AEOSI	%	0.2	0		
Fracture	AEOSI	%	11.7	6.5		
Fall	AEOSI	%	15.6	9.0		
Hypothyroidism	AEOSI	%	8.1	2.0		

Abbreviations: AE (adverse event); AEOSI (adverse event of special interest); TEAE (treatment emergent adverse event)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Apalutamide after failure to ADT has shown a statistically significant difference (25-months increase in median times) in terms of MFS compared to placebo in a population of non-metastatic CRPC patients who had rapidly rising PSA. Results in terms of OS failed to show any statistically significant result and data are still immature so as to firmly conclude about the potential benefit in survival.

The fact of treating patients with apalutamide in the proposed setting implies to delay the metastatic status. This is the main conclusion from the SPARTAN study. To what extent this strategy could add a benefit in OS is for the time being unknown. However, it should be noted that no indication of detrimental effect in OS has been shown.

Additionally, PFS2 results, even immature, are pointing out to a positive result. All in all, from an efficacy point of view, this new treatment represents a valuable option for patients and physicians, even though more mature data are needed. The safety profile of apalutamide could be considered sufficiently characterised. Overall, apalutamide was well tolerated with a manageable safety profile.

3.7.2. Balance of benefits and risks

Results from Spartan trial are considered to demonstrate a statistically significant advantage in terms of MFS for patients with CRPC whereas the safety profile of apalutamide is considered acceptable. Overall, the effect shown in delaying the appearance of metastases overcomes the uncertainties related to lack of maturity of some variables. Therefore, the B/R is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The impact that early introduction of apalutamide treatment may have on cross-resistance development and effect on subsequent treatments is an uncertainty that should be considered in future development.

In order to investigate the long term efficacy of apalutamide in patients with non-metastatic castration resistant prostate cancer (NM CRPC) who are at high risk of developing metastatic disease, the MAH should submit the final results of the SPARTAN study Post Authorisation Efficacy study (PAES).

3.8. Conclusions

The overall B/R of Erleada is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Erleada is favourable in the following indication:

Erleada 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Obligation to conduct post-authorisation measures

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

Description	Due date
Postauthorisation efficacy study (PAES): In order to further evaluate the efficacy of Erleada, the MAH should submit the final clinical study report, including overall survival results, from study ARN-509-003 (SPARTAN) comparing the efficacy and safety of Apalutamide vs. placebo in subjects with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer.	June 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that apalutamide is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.