30 January 2020
EMA/84124/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NUBEQA

International non-proprietary name: darolutamide

Procedure No. EMEA/H/C/004790/0000

Note

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

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List of abbreviations

5-HT	5-hydroxytryptamine (serotonin)
ACAP	proportional change in KA1, KA2 and KA3 upon dosing of capsule formulation
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
AFAST	Proportional change in KA1, KA2 and KA3 upon dosing under fasted conditions
AKR	Member of the aldo-keto reductase family
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ASMF	Active Substance Master Files
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve from time 0 to infinity
AUC(0-12)	AUC from time 0 to 12 hours
$AUC(0\text{-}12)_{ss}$	AUC from 0 to 12 hours after nominal b.i.d. dosing to steady state
AUC(0-48)	AUC from time 0 to 48 hours
AUC(0-72)	AUC from time 0 to 72 hours
AV	Atrioventricular
b.i.d.	Twice daily
BCRP	Breast cancer resistance protein
BMD	Bone mineral density
BMI	Body mass index
BPI-SF	Brief pain inventory – short form
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CNS	Central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
CW	Class Waiver
CYP	Cytochrome P450
CYP17i	Enzyme that inhibits 17 α-hydroxylase/C17,20-lyase
DABE	Dabigatran etexilate
Daro	Darolutamide
DDI	Drug-drug-interaction
DES	Diethylstilbestrol
DLT	Dose limiting toxicity
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
e.g.	For example (exempli gratia)
DSp	Design Space
EBRT	External beam radiation therapy
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate

EMA	European Medicines Agency
EMEA	European Medicines Agency
E_{max}	Exposure reflecting the maximum change from baseline
EOD	Extent of disease
EORTC-QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate cancer module
EQ-5D-3L	European Quality of Life 5-Domain Scale, 3 Level
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FAS	Full analysis set
FaSSIF	Fasted state simulated intestinal fluid
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
FPFV	First patient first visit
$GABA_A$	type-A γ-aminobutyric acid receptors
GCP	Good Clinical Practice
GIST	Gastrointestinal stromal tumour
GLP	Good laboratory practice
GnRH	Gonadotropin-releasing hormone
hAR	Human androgen receptor
HCC	Hepatocellular cancer
HFSR	Hand foot skin reaction
HI	Hepatic impairment
HLGT	High level group term
HLT	High level term
HPLC	High performance liquid chromatography
HSGC	Headspace Gas Chromatography
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Integrated analysis
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonization
ICP-OES	Inductively coupled plasma - optical emission spectrometry
i.e.	That is (*id est*)
IND	Investigational new drug
INN	International nonproprietary name
IR	Infrared
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
LHRH	Luteinizing hormone releasing hormone
LLCI	Lower limit confidence interval
MAA	Marketing Authorization Application
Max	Maximum
MATE	Multidrug and toxin extrusion
mCRPC	Metastatic castration-resistant prostate cancer
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
mHSPC	Metastatic hormone-sensitive prostate cancer
MID	Minimally important difference
Min	Minimum
MLG	MedDRA labelling grouping
MoA	Mechanism of action
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance associated protein 2
MTD	Maximum tolerated dose
n	Number of patients with event

N	Total number of patients (100%);
NA	Not applicable / not available
NC	Not calculated
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-ODWG	NCI organ dysfunction working group
NDA	New drug application
NEC	Not elsewhere classified
nmCRPC	Non-metastatic castration-resistant prostate cancer
NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
mCRPC	Metastatic castration-resistant prostate cancer
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall survival
OVAT	One Variable at a Time
PAR	Proven Acceptable Range
PE	Polyethylene
P-gp	P-glycoprotein
PET	Positron emission tomography
PC	Prostate cancer
PCS	Prostate cancer-related symptom
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive disease / pharmacodynamics
PDCO	Paediatric Committee
PFS	Progression-free survival
PI	Prescribing information
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
Pla	Placebo
PP	Per protocol
PR	Partial response
PS	Performance status
PSA	Prostate-specific antigen
PSADECp	PSA decrease, percentage decrease
PSADT	Prostate-specific antigen doubling time
PT	Preferred term
PVC	Polyvinyl chloride
PY	Patient year
Q	Quartile
QbD	Quality by design
QD	Once daily
QoL	Quality of life
QRS (complex)	The series of deflections in an ECG that represent electrical activity generated by ventricular depolarization prior to contraction of the ventricles
QT	Interval on the ECG from the beginning of the QRS complex to the end of the T wave
QTc	QT interval in ECG corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett’s formula
QTcF	QT interval corrected for heart rate using the Fridericia’s formula
QTPP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
RI	Renal impairment
ROW	Rest of the world
RSE	Relative Standard Error
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAF	Safety analysis set

SAP	Statistical analysis plan
SCE	Summary of clinical efficacy
SD	Stable disease
SmPC	Summary of product characteristics
SOC	System organ class
SPA	Special protocol assessment
SSE	Symptomatic skeletal event
ST segment	Line on the ECG that begins with the end of the QRS complex and ends at the beginning of the T wave
StD	Standard deviation
TEAE	Treatment-emergent adverse event
TFAST	Proportional change in KTR upon dosing under fasted conditions
TTP	Time to progression
UGT	Uridine-5'-diphospho glucuronosyltransferase
UK	United Kingdom
ULCI	Upper limit confidence interval
US	The United States
UV/VIS	Ultraviolet/Visible
VCaP	Vertebral-Cancer of the Prostate
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer AG submitted on 7 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Nubeqa, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 March 2017.

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

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 CW/0001/2015 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.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance darolutamide 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 on the development relevant for the approved indications from the CHMP on 25 April 2014, 28 April 2016, 20 July 2017, and 14 September 2017. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- Regarding the quality development: proposed starting materials; proposed specifications for drug substance and drug product; the approach to characterising release and stability; proposed strategy to qualify final drug product.
- Adequacy of the overall non-clinical pharmacology and toxicology data package to support further clinical development and MAA in the given indication; adequacy of chronic toxicity studies to support MAA; adequacy of genotoxicity testing to characterise the drug product and major metabolite; requirement for reproductive and developmental toxicity and carcinogenicity studies; approach to characterisation of phototoxicity.
- Regarding a proposed randomised, double-blind, placebo-controlled, phase 3 efficacy and safety study men with nmCRPC: definition of the study population; acceptability of the primary endpoint (metastasis-free survival) and supporting secondary endpoints; acceptability of the statistical assumptions and analyses; proposed dose;
- Regarding the clinical development: the evaluation of effects QTc interval and the need for a dedicated QTc clinical study; the requirement for an in vivo DDI study; the approach to characterise drug transporter interactions.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Jorge Camarero Jiménez

The application was received by the EMA on	7 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019

The applicant submitted the responses to the CHMP consolidated List of Questions on	12 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 October 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 November 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 January 2020
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 Nubeqa on	30 January 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Darolutamide is intended for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (prostate specific antigen doubling time (PSADT) of ≤ 10 months and PSA levels ≥ 2 ng/mL).

While most of the early-stage prostate cancer is curable, a subset of men will progress with biochemical recurrence. Prostate cancer becomes a potentially fatal metastatic disease by progressing first to non-metastatic castration-resistant prostate cancer (nmCRPC), 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. Signs of resistance to androgen deprivation therapy (ADT) include rising serum prostate-specific antigen (PSA) level, which represents chemical progression before radiologically detectable metastases. Non-metastatic CRPC patients with PSA doubling time ≤ 10 months (PSADT; the estimated time required for the PSA level to double) have a high-risk of developing metastases.

2.1.2. Epidemiology

Prostate cancer is the 4th most common cancer worldwide, affecting 7.1% of the population, and the 2nd most common cancer in men, affecting 15% of all men[1],[2]. It is the 3rd leading cause of cancer mortality in men in Europe. In 2018, the estimated number of prostate cancer-related deaths in Europe was 107,000[3].

2.1.3. Clinical presentation, diagnosis and stage/prognosis

Non-metastatic CRPC is defined as CRPC in a man with castrate levels of testosterone in the absence of imaged metastases. Approximately 30% of patients with nmCRPC will develop bone metastases within 2 years, with a median overall survival (OS) of approximately 4 years[4]. Bone pain, skeletal-related events, such as spinal cord compression, symptomatic fracture, and surgery or radiotherapy to bone requiring supportive care measures (bone-targeting agents, vertebroplasty, radiofrequency ablation) are serious complications of advanced prostate cancer and major causes of morbidity and increased mortality[5],[6].

[1] IARC. International Agency for Research on Cancer (IARC), Global Cancer Observatory (GCO). All cancers. Source: Globocan 2018.
[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
[3] Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356-87.
[4] Tombal B. Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? Ann Oncol. 2012;23 Suppl 10:x251-8
[5] Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castrationresistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-22.
[6] Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012;379(9810):39-46.

Among men with nmCRPC, a shorter PSA doubling time (PSADT) is associated with a shorter time to metastasis and death. Patients with a PSADT of ≤10 months and an increasing PSA level are considered at high risk of developing metastatic disease[7],[8],[9].

The delay of metastases and the associated morbidity for as long as possible is the goal of therapy for men with nmCRPC.

2.1.4. Management

Despite initial responses of 80-90%, nearly all men develop progressive disease following ADT, referred to as castration-resistant prostate cancer (CRPC)[10].

CRPC remains mainly driven by the AR signalling pathway and high-level AR expression commonly occurs in CRPC[11],[12]. Until recently there were no medicinal products approved for the treatment of nmCRPC at high risk of developing metastasis and the National Comprehensive Cancer Network (NCCN) guideline recommended first-generation antiandrogens (e.g., bicalutamide, nilutamide, flutamide), second-generation novel hormonal therapies (enzalutamide, abiraterone), ketoconazole, corticosteroids or diethylstilbestrol as second-line hormonal therapies[13] while the European Society for Medical Oncology guidelines refers to ADT and watchful waiting[14]. However, recently two nonsteroidal anti-androgens, apalutamide and enzalutamide have been approved for treatment of nmCRPC at high risk of developing metastases in EU[15],[16]. Available data showed that enzalutamide (PROSPER trial) and apalutamide (SPARTAN trial), respectively, improved metastasis-free survival (MFS) compared to placebo among patients continuing ADT for nmCRPC[17],[18]. The AR inhibitors enzalutamide and apalutamide were shown to provide significant MFS benefit to nmCRPC patients with PSADT of 10 months or less, but resulted in increased risk of toxicities including seizures, falls, fractures, hypertension, weight loss, cognitive disorders, fatigue and rash when used along with ADT[18,19].

About the product

Darolutamide is an androgen receptor (AR) inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain.

[7] Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol. 2005;23(13):2918-25.
[8] Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol. 2013;31(30):3800-6.
[9] Smith MR, Cook R, Lee KA, Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer. 2011;117(10):2077-85.
[10] Dai C, Heemers H, Sharifi N. Androgen Signaling in Prostate Cancer. Cold Spring Harb Perspect Med. 2017;7(9).
[11] Linja MJ, Savinainen KJ, Saramaki OR, Tammela TL, Vessella RL, Visakorpi T. Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer. Cancer Res. 2001;61(9):3550-5.
[12] Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28.
[13] NCCN 2017
[14] Parker et al, 2015
[15] EPAR Xtandi
[16] EPAR Erleada
[17] Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-74.
[18] Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-18.

Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. Darolutamide treatment decreases prostate tumour cell proliferation leading to potent antitumour activity. (see SmPC section 5.1).

The recommended indication is: Nubeqa is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see SmPC sections 4.1 and 5.1).

Treatment should be initiated and supervised by a specialist physician experienced in treatment of prostate cancer.

The recommended dose is 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg.

Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

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 because there were available therapies (apalutamide and enzalutamide) with positive benefit/risk balance for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease and thus medical need could not be considered unmet. Although it is considered valuable having additional therapeutic options for the treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease, this was not considered sufficient to trigger accelerated assessment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 300 mg of darolutamide.

Other ingredients are: Tablet core; calcium hydrogen phosphate (E 341), croscarmellose sodium, lactose monohydrate, magnesium stearate (E 470b), and povidone K 30 (E 1201). Film coating; hypromellose 15 cP, lactose monohydrate, macrogol 3350 (E 1521), and titanium dioxide (E 171).

The product is available in PVC/Aluminium foil blisters containing 16 film coated tablets as described in section 6.5 of the SmPC. Each pack contains 112 film-coated tablets.

2.2.2. Active Substance

General information

The chemical name of darolutamide is N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan -2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide corresponding to the molecular formula $C_{19}H_{19}ClN_6O_2$. It has a relative molecular mass of 398.85 g/mol and the following structure:

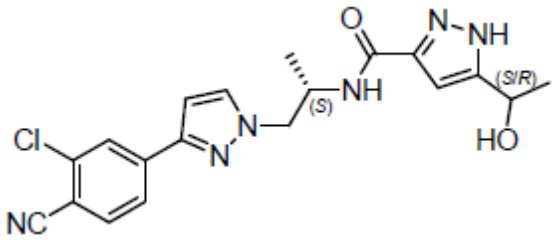


Figure 1: active substance structure

The chemical structure of darolutamide was elucidated by a combination of IR, Raman UV/VIS, 1H-NMR, 13C-NMR and mass spectroscopy. An analysis of the solid state properties including possible polymorphs and a discussion of the stability of the polymorphic form in the active substance was provided.

The active substance is a white to greyish- or yellowish-white powder which his not hygroscopic. The active substance solubility is very low; darolutamide is practically insoluble in water and in the pH range from 1.0 to 6.5, as well as in fasted state simulated intestinal fluid (FaSSIF) pH 6.5; very slightly soluble in FaSSIF pH 5.0.

Darolutamide exhibits stereoisomerism due to the presence of two chiral centres. The configurations are (S, S)-darolutamide and (S, R)-darolutamide. Darolutamide milled active substance is a mixture of diastereomers (S, S)-darolutamide and (S, R)-darolutamide. These were consistently obtained through the synthesis pathway, as a 1:1 mixture. The diastereomeric ratio of all darolutamide milled active substance batches used in clinical studies has been consistent and is controlled routinely in the active substance specification by a chiral HPLC test. *In vivo*, the diastereomers interconvert via the metabolite keto-darolutamide.

Darolutamide exhibits polymorphism. Form I is the thermodynamically stable polymorph at ambient conditions and the active substance manufacturing process is designed to produce crystal form I. The identity of crystal form I is controlled routinely in the active substance specification by X-Ray powder diffraction (XRPD) test.

Manufacture, characterisation and process controls

Darolutamide is synthesized in six main steps (four chemical transformations, crystallization and physical treatment by milling) using well defined starting materials with acceptable specifications. Adequate detailed description of the active substance synthesis process was provided in the dossier.

The choice of starting materials has been justified in line with the requirements of ICH Q11 guideline. The quantities of reagents described in the manufacturing process are specified for a typical batch size and can be

adapted to the size of the apparatus, etc. provided the stoichiometric ratio of the reaction components remains constant.

The manufacturing process has been developed using a combination of conventional univariate studies such as One Variable at a Time (OVAT) studies and elements of QbD such as risk assessments and design of experiment (DOE) studies. Design Spaces (DSp), Proven Acceptable Ranges (PARs) and Normal Operating Ranges (NORs) are set in the different steps of the commercial active substance manufacturing process.

During development, the process parameters were evaluated by risk assessment and the process parameters with potential influence on the quality attributes of darolutamide were identified and investigated by OVAT studies or by performing multivariate studies (DoE). During the marketing authorisation application (MAA) procedure a major objection was raised relating to a significant number of PARs which required further justification and/or supporting data and to discrepancies between the PARs described in the development (3.2.S.2.6) and manufacturing sections (3.2.S.2.2) of the dossier. In responses the applicant provided additional data from multivariate DoE studies where the effects of all potentially interacting process parameters were investigated. The studies conducted in each step were described. The parameters used for the results interpretation in the different studies have been justified. In addition, the potential interaction between parameters and scalability issues have also been considered.

Based on those studies Design Spaces and multiple PARs were defined in various process steps. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical process parameters that impact the active substance properties have been described, in particular the reaction conditions that could lead to impurities present in the final active substance. Specifications used for the controls of the intermediates have been provided, as well as batch results.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed Design Spaces and PARs.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities, including potentially genotoxic impurities, were well discussed with regards to their origin and potential carryover to the active substance.

The active substance is packaged in transparent low density polyethylene (PE) foil which complies with Ph. Eur. chapter 3.1.4 and EC 10/2011 as amended. The secondary packaging is a PE bag placed in a closed container (e.g. fibre drum).

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC), organic impurities (HPLC), diastereomeric ratio (HPLC), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), residual solvents (HSGC), particle size distribution (laser diffraction), polymorphism (XRPD), microbiological impurities (Ph. Eur.) and palladium (ICP-OES).

The limits for the control of impurities are in line with the batch results. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The impurity keto-darolutamide is above the qualification limit according ICH Q3A; nevertheless, since it is also a major human and animal metabolite of the active substance it can be considered qualified.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from four commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 production batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: assay, impurities, loss on drying, diastereomeric ratio, particle size distribution and polymorphism. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and were similar between the batches, with the exception of out of specification results observed for the particle size distribution for some of the batches. Further investigation was performed confirming that the out of specifications results obtained were explained by an agglomeration of the particles in the small packaging used for the storage of the active substance during the stability study. No change in the particle size distribution was observed in the bulk packaging.

No trends are observed for the other parameters tested, neither for impurities nor the diastereomeric ratio. The polymorphic form of the active substance is maintained throughout the storage period.

Results from stress-tested conditions (thermal, humidity, oxidative, hydrolytic alkaline and hydrolytic acidic) were also provide in order to investigate the formation of potential degradation products. The samples were tested for assay, specified impurities and unknown impurities. The observed unknown degradation products are sufficiently separated from the active substance peak or peak of specified organic impurity; the peak of the active substance did not show any sign of co-elution with the degradation products.

A photostability study was performed according to ICH Q1B. No significant degradation was observed on the solid substance, the assay showed no significant decrease. However, some degradation was observed when the active substance was in solution. It was concluded that no special protection from light is necessary during the production or handling of the solid active substance, however the active substance solutions used in the HPLC assay and impurities analysis should be protected from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months without any special storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as white to off-white, oval, film-coated tablets, marked 'BAYER' on one side and '300' on the other side, packed in a blister. The dimensions of the tablets are 16 mm length, 8 mm width, 5 mm thickness and the tablet weight is 618.0 mg.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

A Quality by Design (QbD) approach was applied in the development of the formulation and manufacturing process in line with the principles of ICH Q8. The quality target product profile (QTPP) was defined as an immediate release tablet, film-coated to facilitate swallowing and protect from direct contact with the drug substance, that meets pharmacopoeial and other relevant quality standards (e.g. ICH), and is packaged to provide suitable protection of the product.

The critical quality attributes were identified. Additional quality attributes of the granules and/or tablet cores, important for formulation and process development were also identified.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. An initial risk analysis was performed using the Failure Mode Effect Analysis (FMEA) method to define critical process steps and process parameters of each manufacturing step that may have an influence on the critical quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies.

Several process development studies focusing on the identified risks were performed on laboratory, pilot and commercial scale batches. Subsequently, an intermediate risk analysis was conducted, considering the increased process and product understanding. Critical manufacturing steps and material/process parameters were identified. The manufacturing process development investigated several ranges for some of the manufacturing steps, which could interact with each other. Justification for these ranges is supported by the development studies, including multivariable studies performed at a laboratory scale.

An optimal control strategy was defined for the finally identified as high-risk process parameters / material attributes so that all possible risks were reduced to an acceptable level. The studies and the analysis performed are comprehensive, a good understanding of the manufacturing process and product attributes has been demonstrated. The critical manufacturing steps, materials attributes and process parameters selected are justified. The studies performed and results obtained demonstrate that other parameters are less critical, within the ranges evaluated. There are three manufacturing steps in which more than one process parameter range is specified. These process parameter ranges are classified as Design Spaces (DSp), PARs or NORs.

The final formulation selected is in accordance with the properties of the active substance and the QTPP. The choice of the excipients has been adequately justified, in terms of the qualitative and the quantitative composition. The active substance contained in the finished product is a mixture of two diastereomers. The proportion was demonstrated not to be affected by the finished product manufacturing process and to remain constant during the shelf life of the product. Similarly, the same polymorphic form of the active substance is

used in the manufacturing process and is contained in the finished product. Milled active substance, with a controlled particle size, is used in the composition of the finished product, as the particle size can impact the dissolution of the tablets.

The active substance is considered to be a BCS class 2 active substance, having a low solubility and high permeability. The discriminatory power of the proposed dissolution method has been demonstrated and considered to be acceptable.

During development, an oral solution and an intravenous solution were used in a phase I mass balance, PK, biotransformation and bioavailability study. A capsule formulation was used in phase I and phase II clinical studies. An uncoated tablet formulation was developed and used in a further phase I study. Film coated tablets were developed for phase III and the commercial phase. The core composition of the uncoated tablet and the final tablet are similar, with the exception of the magnesium stearate concentration , compensated by amounts of lactose monohydrate and calcium hydrogen phosphate. For the clinical studies a blue coating film was used. For the commercial tablet the blue coat was replaced by a white coat. Similarity of exposure between the capsule and the uncoated tablet was demonstrated in a phase I bioavailability study at 600 mg dose. The application of the blue film was demonstrated to have no relevant effect on dissolution and the change of the film from blue to white was demonstrated to result in similar dissolution profiles.

The primary packaging is PVC/Aluminium foil blister strips containing 16 film coated tablets each. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of a number of steps including; mixing, granulation, drying of granules, mixing and lubrication, tablet compression and film-coating. The manufacturing process is considered to be a standard process and is justified by the properties of the active substance and the target profile of the drug product.

A detailed narrative description of the manufacturing process is provided in the dossier. The controls of the critical steps were presented. There are three manufacturing steps in which more than one process parameter range is specified. These process parameter ranges are classified as Design Spaces (DSp), PARs or NORs.

The design spaces have been developed at lab/pilot scale. The extrapolation of the laboratory scale observations to pilot scale has been justified and the extrapolation to production scale batches is based on evaluation of the observations made on the batches manufactured over time. The ranges used in the description of the finished product manufacturing process are justified by the studies performed during the pharmaceutical development. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space and PARs.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form and are justified by the development studies performed.

A holding time is specified for the bulk product packed in double polyethylene bag placed in tightly closed tin containers. This is considered acceptable, as holding time study results were provided to support the proposed period. The applicant has confirmed that the expiration period of production batches will be set considering the principle defined in the *Note for Guidance on start of shelf-life of the finished dosage form*.

Production scale batches have been manufactured. As the finished product manufacturing process is a standard process, the proposal to perform the validation of the manufacturing process at maximum commercial scale on three batches on each granulation lines before the release of the batches and the controls planned during this exercise are acceptable.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; appearance, identity (HPLC, UV/VIS), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), degradation products (HPLC), assay (HPLC) and microbial purity (Ph. Eur).

The finished product is released on the market based on the release specifications, through traditional final product release testing. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The limits proposed for the control of the degradation products were tightened in response to questions raised during the MAA procedure. The limit for unspecified degradation products has been set in line with the requirements of ICH Q3B. The limit proposed for total impurities is in line with the batch results found in the stability studies.

The limit for the control of the dissolution was tightened in response to questions raised during the MAA procedure. This acceptance criteria is in line with the batch results and is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on four commercial finished product batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Batch analysis results were provided for three finished product batches. The results were similar between the batches and compliant with the acceptance criteria in the finished product specification. In addition, batch results from representative batches used in technical, clinical and/or stability studies are provided in the documentation.

Stability of the product

Stability data from three batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (Al/PVC blisters).

Samples were tested for appearance, assay, degradation products, dissolution and microbial purity. The analytical procedures used are stability indicating. The results obtained under long-term, intermediate and accelerated stability conditions demonstrate that the finished product is stable. No particular trend was observed. As there were no significant changes observed during the period of the stability study, an extrapolation of 12 months is possible, according to the ICH Q1E guideline.

In addition to the data from the primary stability studies, supportive stability data from batches used in clinical trials, at long-term and accelerated conditions, were provided. As these batches were packaged in HDPE bottles they were not considered for setting the product shelf-life.

The stability of the tablets in bulk has been studied. The 12-months bulk stability data for two batches at long-term conditions were adequate to support the proposed bulk holding time.

The results obtained in additional studies (i.e. open container, photostability studies) confirm the stability of the product. No changes in any of the tested parameters indicating any light sensitivity of the product were observed.

A forced degradation study of the finished product was carried out to get information on the degradation of the active substance darolutamide in the formulation.

Post-approval stability commitments to continue the primary stability studies up to 36 months and to perform stability studies on the first three commercial scale batches up to at least 36 months at long-term and 6 months at accelerated storage conditions are provided.

Based on available stability data, the proposed shelf-life of 3 years (36 months) when stored in the commercial packaging with no special storage conditions, as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

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.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance and finished product. The design spaces have been adequately verified.

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. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress and to investigate the risk of presence of nitrosamine in their medicinal products, the CHMP recommends the following points for investigation:

- It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities in Nubeqa (darolutamide) is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacology non-clinical data for darolutamide included a description of *in vitro* activity and mechanism of action. Furthermore, *in vivo* pharmacology data derived from different human prostate cancer models implanted on mice were provided. The secondary pharmacodynamics and safety pharmacological profile of darolutamide and, in selected cases, (S,R)-darolutamide, (S,S)-darolutamide, and keto-darolutamide, was assessed in various *in vitro* and/or *in vivo* (rat, dog; single dose) studies. Vital organ functions including central nervous system, cardiovascular system (including ECG) and respiratory system as well as on supplementary organ systems (gastrointestinal tract) were investigated.

Non-clinical pharmacokinetic studies exploring the ADME (absorption, distribution, metabolism and excretion) characteristics and the toxicokinetic profile of darolutamide were provided.

The toxicological program included studies to investigate the systemic toxicity and exaggerated pharmacodynamic effects after repeated administration to rats and dogs as well as studies addressing a potential genotoxicity and phototoxicity of darolutamide.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Table 1: Summary of *in vitro* primary pharmacodynamics studies

Study type / study number	Objectives	Test system/ method	Noteworthy findings

Binding affinity of ORM-15674 to rat androgen receptor **R-9750**	To characterize the inhibitory activity of Darolutamide, its metabolites and diastereomers against rAR and to compare their inhibitory activity with Bicalutamide.	• ORM-15674 (darolutamide) ORM-15341 (active metabolite) ORM-16497 ((S,R)-Darolutamide) and ORM-16555 ((S,S)-Darolutamide) ORM-10271 (Bicalutamide) • Chemicals and reagents: Mibolerone Testosterone Triamcinolone acetonide • Ventral lobes of prostates from male rats • Binding affinities were measured by competition binding assay • Analysis of data: Saturation binding Competitive binding	• Ki values for ORM-15674, ORM-15341, ORM-16497, and ORM-16555 to rat androgen receptor were 9.1nM, 7.5nM, 9.3nM and 18.6nM respectively. • This Ki values were comparable to the value determined for non-steroidal anti-androgen Bicalutamide, which was 12.1nM. • This binding affinity results indicate that ORM-15674, its diastereomers and metabolite interact with rat AR with high binding affinity.
Functional activity of ORM-15674 to androgen receptor **R-9751**	To measure the potency and functional activity of Darolutamide, its diastereomers and metabolite against hAR in HEK293 cells and to compare their potency with Bicalutamide.	• Reporter gene assay in HEK293 cells transfected with an expression vector encoding hAR and androgen responsive luciferase reporter gene construct • Reporter gene assay HS-HEK293 A clone expressing 5 times more AR than AR-HEK293 cells)	• ORM-15674, its diastereomers and metabolite are potent and full hAR antagonists with IC50 values of 65nM, 25nM, 38nM and 51nM respectively. Bicalutamide is less potent antagonist for hAR with IC50 value of 150nM. • Bicalutamide showed antagonist activity (66% inhibition) in AR-HEK293 cells but it has a weak antagonist activity at µM concentrations in the HS-HEK293 cells (maximum of 38% inhibition at 1µM). • In addition, >100 nM concentrations of Bicalutamide showed clear agonistic activity (up to 72% stimulation) • In contrast, ORM-15674 was found to have clear agonist activity only at concentrations >3µM in AR overexpressing HS-HEK293cells. • Both diastereomers showed significant antagonistic activity and only modest agonist activity in the AR overexpressing HS-HEK293 cells. The metabolite also functions as an antagonist (up to 72% inhibition) in HS-HEK293 cells.
Inhibition of androgen receptor nuclear translocation by ORM-15674 **R-9752**	To investigate the capacity of ORM-15674 to inhibit the androgen nuclear transfer to the nucleus from the cytoplasm.	• AR-overexpressing cell clone HS-HEK293 • Plates were imaged with Cellomics Arrayscan VTI • Images were analyzed with NucTrans.V3 Assay Algorithm	• In the presence of Bicalutamide, AR was largely nuclear (>50%) at concentrations greater than 0.2µM. • In the presence of ORM-15674 and ORM-15341, AR was predominantly nuclear only in

			the presence of high concentrations of both ORM-15674 and ORM-15341 (>5µM and >1µM respectively). ➢ Bicalutamide was 25-times more potent than ORM-15674 and 5-times more potent than ORM-15341 in inducing AR nuclear localization. • ORM-15674 and ORM-15341 were found to decrease 0.3nM testosterone-induced nuclear localization at concentrations > 100nM and > 300nM respectively. • Bicalutamide failed to block testosterone-induced AR nuclear localization at all tested concentrations.
Transactivation of mutant androgen receptors by ORM-15674 **R-9753**	To measure the capacity of Darolutamide and its metabolite to inhibit AR mutants AR(T877A) and AR(W741L) in transactivation assay and to compare the results with second-generation antiandrogens Enzalutamide and ARN-509	• Human U2-OS osteosarcoma cell line • Transfected with androgen-responsive reporter gene construct and expression vectors encoding AR mutants AR(T877A) or AR(W741L) • Cell suspension combined with DNA-LipofectamineTM2000 complexes • Agonistic reference compounds: testosterone and DHT	• Bicalutamide, ORM15674 and its metabolite all suppressed testosterone-induced transcriptional activity of T877A mutant AR with IC50values 0.8, 2.6, 1.4µM respectively. • Bicalutamide acts as a pure agonist on the W741L substitution with an IC50 value of 10nM. • ORM-15674 and its metabolite functioned as antagonists for AR(W741L) with IC50 values 1.1 and 1.1 µM.
Transactivation of the mutant androgen receptor hAR(F876L) by ODM-201 **R-9754**	To measure the capacity of Darolutamide and its metabolite to inhibit the missense mutation F876L in transactivation assay and to compare the results with Bicalutamide.	Test compounds: ODM-201 (1:1 mixture of the two diastereomers (S,R) and (S,S)) and ORM-15341 • Reference compounds: enzalutamide and ARN-509 (apalutamide) • Human U2-OS osteosarcoma cells • Transfected with androgen-responsive reporter gene construct and expression vectors encoding AR mutant (F876L) • Agonistic reference compounds: testosterone and DHT	• ODM-201 and its metabolite suppressed testosterone-induced transcriptional activity of F876L mutant AR with IC50 values of 85 and 47nM respectively). • Both reference compounds: Enzalutamide and ARN-509, functioned as partial agonists. • The maximum agonism of Enzalutamide to AR(F876L) was 43% and that of ARN-509 70% of the transcriptional activity of testosterone 100%.
Inhibition of VCaP cell proliferation with ORM-15674 **R-9755**	To measure the ability of Darolutamide and its metabolites to inhibit prostate cancer cell growth and to compare the results with Bicalutamide	• ORM-15341 and ORM-15674 • VCaP prostate cancer cell line • WST-1 Cell Proliferation Assay to measure cell proliferation	• ORM-15674 and its metabolite suppressed dose dependently androgen-induced VCaP cell proliferation (>95%). • Bicalutamide was able to antagonize growth only partially (65%). • The IC50 values for ORM-15341 and its metabolite were 0.6 and 0.5µM respectively. • The IC for Bicalutamide was 1.2µM

In vivo

Table 2: Summary of *in vivo* primary pharmacodynamics studies

Study type / study number	Objectives	Test system/ method	Noteworthy findings
Antagonism of ORM-15674 and ORM-15341 against androgen receptor stimulation with testosterone propionate in immature rats **R-9756**	To investigate the antagonism of ORM-15674 and its metabolite against androgen receptor in immature male rats treated at submaximal dose of testosterone	• Immature male Sprague Dawley rats • ORM-15674: 10,30,100 mg/kg • ORM-15341: 10,30 mg/kg • 6 days • Testosterone propionate • Daily administration • Per os	• When administrated with testosterone propionate, both ORM-15674 and ORM-15341 showed antagonistic features by decreasing significantly and dose-dependently the relative mass of the ventral prostate and the relative mass of seminal vesicles compared to mere testosterone dosing. • Relative weight of ventral prostate was reduced by 50, 78 and 110% following oral, daily treatment with 10, 30 and 100mg/kg of darolutamide, in comparison to the 3mg/kg, s.c, daily TP-stimulated group. • Relative weight of seminal vesicles was reduced by 33, 63 and 88% following oral, daily treatment with 10, 30 and 100mg/kg of darolutamide, in comparison to the 3mg/kg, s.c, daily TP-stimulated group.
Effects of ORM-15674 on the growth of SC, xenografted VCaP tumours in nude mice, comparison with reference compound ORM16678 **R-9762**	To test whether drug treatment can prevent or delay tumor re-growth after tumour growth has initially been suppressed by orchidectomy (ORX) in condition when tumour growth in castration resistant prostate cancer (CRPC) escapes from the first treatment	• Balb/c nude mice (xenograft model) • VCaP prostate cancer cell line • ORM-15674 50mg/kg • Once or Twice daily oral dosing • ORM-16678 20mg/kg for 37days	• Xenografted tumours were observed to grow significantly more slowly in mice treated for 37 days with 50mg/kg of darolutamide, orally, once daily, compared to castrated untreated mice. • When treating mice twice daily with 50mg/kg darolutamide for 37 days, tumour regression was observed, compared to castrated untreated mice. The tumour regression was higher than once daily treatment.
The effects of ORM-15674 on the growth of orthotopic VCaP tumours in nude mice, comparison with reference compound-ORM-16678 **R-9760**	To examine the efficacy of ORM-15674 for its effects on the growth of PC tumours in intact nude male mice and to compare the effect with the reference compound ORM-16678 (enzalutamide). In addition, the effects on serum PSA and testosterone levels and several relative weights were determined.	• Mouse (nude BALB/c) • VCaP cells • 50 mg/kg darolutamide • Twice daily oral dosing • 3 week treatment	• VCaP cells were inoculated into the prostate of nude intact male mice • Both ORM-15674 and ORM-16678 had no effects on the body weights of the mice during the study period. • ORM-15674 significantly decreased the volume of VCaP tumours. No significant decrease was observed with ORM-16678. • No significant changes in tumour weights of VCaP tumours were observed for both ORM-15674 and ORM-16678. • ORM-16678 at 20mg/kg/day increased the relative weight of testis significantly as well as ORM-15674 at 50mg/kg/twice daily. • ORM-15674 at 50mg/kg/twice daily significantly decreased the relative weight of kidney. • ORM-15674 and ORM-16678 significantly decreased the serum PSA levels from day 42/44 of the study period**.** • No significant changes in serum testosterone levels were observed in treatment groups compared to vehicle group. A trend of increased serum testosterone levels could be detected with ORM-16678.

Effects of ORM-15674 on the growth of orthotopic, castration-resistant VCaP tumours in nude mice R-9761	To examine the antitumourigenic activity of the novel antiandrogen ORM-15674 in the castration-resistant VCaP ortograft model	• Mouse (nude BALB/c) • VCaP cells • 25, 50, 100mg/kg Darolutamide • Twice daily oral dosing • 4 week treatment • Tumour volume estimation by ultrasound	• VCaP cells were inoculated into the prostate of castrated mice. • ORM-15674 had no significant effects on the tumour weights of the mice (high variation in the individual tumour size) but a clear dose-dependent trend of inhibition of tumour growth was detected. • ORM-15674 with tested doses had no effects on the tumour volumes, on the body weights, on liver, lung, spleen or kidney weights. • ORM-15674 inhibited mean relative PSA growth with all doses compared to the vehicle. • ORM-15674 with the doses 50 and 100mg/kg twice daily showed significant difference in serum PSA levels compared to control group. • ORM-15674 showed a dose-dependent trend to inhibit the growth of the orthotopic VCaP tumours in the castration-resistant prostate cancer model.
Assessment of PK/PD relationship	To estimate the efficacious AUCs in the animal pharmacology studies based on the systemic exposure determined in mimicking studies in mice following administration of the efficacious doses in xenografts.	• Mice xenografts • 25/50 mg/kg twice daily	• The lowest dose of 25 mg/kg bid maximally suppressed PSA in mice. • Based on a free Darolutamide fraction of 8.0% in human plasma these efficacious exposures correspond to unbound AUC(0-24) at steady state of 4610 and 5408 ng·h/mL, respectively. • These values are similar to the mean unbound AUC (0-24) in mice after a dose of 25 mg/kg bid, which showed to be maximally efficacious for suppressing PSA.

Secondary pharmacodynamic studies

Table 3: Summary of secondary pharmacodynamics studies

Study type / study number /	Test system/ method	Noteworthy findings

Receptor binding and enzyme assays **R-9872** **R-9874** **R-9873**	• Darolutamide, (S,R)-Darolutamide, (S,S)-Darolutamide and keto-Darolutamide • Concentration up to 10µM (in duplicate) • Over 100 enzymes and receptors	• Darolutamide: binding for human progesterone receptor (hPR), rat central benzodiazepine receptor (rBZD), human serotonin transporter (h5-HT transporter). • Significant binding (>50%): o Human progesterone receptor (hPR): 76% inhibition at 10 µM o Rat central benzodiazepine receptor (rBZD): 58% inhibition at 10 µM o Human serotonin transporter (h5-HT transporter): 85% inhibition at 10 µM • (S,R) and (S,S)-Darolutamide: binding for rBZD (central, 48% and 27% inhibition at 5 µM, respectively) and h5-HT transporter (56% and 64% inhibition at 5 µM, respectively) • Keto-Darolutamide: binding for adenosine receptor A3 (53% inhibition at 10 µM), hPR (62% inhibition at 10 µM) and h5-HT transporter (86% inhibition at 10 µM).
Transactivation assays **R-9876**	• Ability of ORM-1 5674, ORM-15341 and Bicalutamide to influence PR-mediated transcriptional activation measured in human osteosarcoma cell line (U2-OS)	• ORM-15674, ORM-15341 and Bicalutamide are PR antagonist and had IC50 values of 5.1µM, 4.5µM and 4.1µM respectively in the presence of 10µM progesterone
R-9871	• Rat brain synaptosomes • Darolutamide (from 1nM to 10µM)	• Darolutamide concentration-dependently inhibited 5-HT uptake with an IC50 value of 3.4µM • Imipramine had an IC50 of 62nM
Functional *in vitro* assays **R-9875**	• Darolutamide and keto-Darolutamide: 3,10,30µM • Patch clamp assay in isolated rat striatal neurons	• IC50 of Darolutamide and keto-Darolutamide inhibition of GABAa were 5.5µM and 3.4µM respectively

Safety pharmacology programme

Safety pharmacology studies were conducted in line with ICH S7A and S7B guidelines. Most of them were performed according to GLP, except the *in vitro* studies (electrophysiology).

Central Nervous System

Evaluation of the potential effects on CNS was done during the 4-week toxicity study in rats. Darolutamide was given at 100, 300, or 1000 mg/Kg/day by oral gavage. No effects were reported, except a reduced motor activity in males and females, and reduced alertness in males at ≥300 mg/Kg/day at week 3. The mean maximum concentrations (C_{max}) values of darolutamide and keto-darolutamide at the highest dose of 1000 mg/kg/day at Day 1 were 22100 and 23500 ng/mL in males and 29000 and 25000 ng/mL in females, respectively.

Respiratory system

Respiratory parameters were evaluated by plethymosgraphy method after single dose (oral gavage) in rats. The animals were dosed with darolutamide at 100, 300, or 1000 mg/Kg, and respiratory rate, tidal volume and respiratory minute volume were recorded. Decreased tidal volumes (-32% at 5 h and -24% at 24 h, compared

to vehicle) and respiratory minute volume (-25% at 5 h and 18% at 24 h, compared to vehicle) in 1000 mg/kg dosed animals, at 5 and 24 h post-dose, were considered incidental and not treatment-related.

Gastrointestinal effects

The charcoal propulsion test was used to evaluate the potential effects of darolutamide (30, 100, 300 and 1000 mg/Kg) on intestinal motility and gastric emptying. No effect was reported up to the highest dose level tested, administered as a suspension. Insoluble test article was found in the intestines in animals given at ≥300 mg/Kg.

Cardiovascular effects

In the *in vitro* automated patch clamp assay (non-GLP), darolutamide showed a weakly inhibition against hERG. Darolutamide, (*S,R*)-darolutamide, (*S,S*)-darolutamide, or keto-darolutamide were tested at the concentrations of 1, 3, 10 and 30 μM. The IC_{50} values reported for the four test compounds were 87.9, 11.5, 30.2, and 8.0 μM, respectively. Darolutamide blocked the hERG current by 34.5% at the highest dose (30μM).

In vitro, darolutamide dose-dependently inhibited the L-type calcium channel (non-GLP assay). The IC_{50} values obtained were 37.4, 42.5, 46.6 and 22.5 μM, respectively for darolutamide, (*S,R*)-darolutamide, (*S,S*)-darolutamide, and keto-darolutamide. These values were compared to those obtained with bicalutamide and calcium channel blockers (verapamil and dihydropyridine), 12.9, 4.1 and 0.6 μM, respectively.

Table 4: *In vivo* safety pharmacology - summary of cardiovascular effects

Study type / study number / literature	Test system/ method	Noteworthy findings
Cardiovascular (anesthetized Beagle dogs) **R-9691** **R-12429**	• Beagle Dogs • IV bolus injections • Darolutamide (ODM-201) concentrations: 0,3,10 and 20mg/kg	**>10 mg/kg:** o Dose-dependent vasodilatation o Decreased arterial blood pressure o Increased mean coronary flow **20 mg/kg:** o Increased cardiac output o Slight and brief shortening in ventricular repolarization duration o Decreased in arterial blood pH o Report R96-9691**: decreased in QT** interval duration briefly observed • **NOAEL = 3mg/kg** • The analytes are the diastereomers ORM-16555 and ORM-16497 and the metabolite ORM-15341. In addition plasma concentrations of ODM-201 (the sum of diastereomers) were calculated.
Cardiovascular (anesthetized Beagle dogs) **R-9690** **R-12430**	• Beagle Dogs • IV bolus injections • (S,S) Darolutamide (ODM-16555) • concentrations: 0,1,3,10 mg/kg	**1 mg/kg:** o Slight decrease in arterial blood pressure and mean femoral flow **>3 mg/kg:** o Marked vasodilatation o Dose-dependent decrease in arterial blood pressure o Decreased in systolic left ventricular pressure and cardiac output o **Slight shortening in ventricular repolarization duration (in QT and heart rate-corrected QTc interval duration)** **10mg/kg:** o Increased mean coronary flow o 1 dog out of 4 displayed a reversible atrioventricular nodal abnormality (complete AV block). PQ and PR interval remained prolonged o No change in heart rate attributable to the treatment with (S,S) Darolutamide was observed **NOAEL = 1mg/kg**
Cardiovascular repeat-dose Toxicity study (conscious Beagle Dogs) **518001/R-9667** **AB14462/R-9672**	• Darolutamide suspension (ORM-15674 mixture of the 2 diastereomers and the metabolite) once daily • 28-day study • Darolutamide concentrations: 0,50,200,800mg/kg • Conventional ECG recording	• Systolic, diastolic and mean arterial blood pressure were unaffected • No changes in gross morphology in ECG or rhythm • No changes in any of the measured parameters of ECG including PR, QRS and QT interval and heart rate-corrected QT values

AB19526/R-9679	• Darolutamide (suspension) twice daily • 13-week study • Darolutamide concentrations: 0,25,75,200mg/kg • Telemetry	
	• Darolutamide (suspension) twice daily • Darolutamide concentrations:0,25,75,200mg/kg • 39-week study • Conventional ECG recording	

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were submitted (see discussion on non-clinical study).

2.3.3. Pharmacokinetics

Methods of analysis

The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

Absorption

In vivo single dose PK

After single oral administration of darolutamide, the absorption was complete, and the absolute bioavailability was high in rats (100%). The bioavailability in dogs was low in fasted (12.6%) and in fed state (16.3%). The slightly higher value in fed state was attributed to a food effect. Darolutamide exposure in terms of AUC(0-24) increased less than dose-proportionally in both species in the dose range tested, especially from mid to high dose, supporting the assumption of solubility-limited absorption from suspensions.

After IV administration of darolutamide the AUC ratio of keto-darolutamide to darolutamide amounted to 1:1 in both species. The plasma clearance (CLP) of darolutamide was low in male rats with 0.46 L/(h·kg) and the apparent CL with 0.19 L/(h·kg) in dogs. In rats whole blood clearance (CLB) was 0.71 L/(h·kg) and in dogs the apparent CLB was 0.39 L/(h·kg) and thus, 21 and 16% of the corresponding liver blood flow (rat: 4.2 L/(h·kg), dog: 2.1 L/(h·kg)).

The CLp of the two diastereomers in rats was in the same range (0.41 – 0.53 L/(h·kg)), whereas in dogs the apparent CLp of (S,R)-darolutamide with 0.11 L/(h·kg) was much lower as compared to (S,S)-darolutamide (0.70 L/(h·kg) indicating faster elimination of (S,S)-darolutamide. The volume of distribution (Vss) of darolutamide was high in rats with 1.16 L/kg and in dogs with the apparent Vss of 1.8 L/kg. The plasma elimination half-lives were long in rat, dog (apparent) and human (t1/2: 4, 7 and 12 hours, respectively).

In vivo repeated dose PK

In male mice, at a daily oral dosing of 25, 50, 100 mg/kg/day for 7 days the apparent steady state exposure in terms of AUC(0-24) and Cmax increased from the low to the high dose less than dose-proportional. The diastereoisomeric ratio at steady state for AUC (0-24) was on average 0.8:0.2. The metabolite/parent ratio for AUC (0-24) increased with dose from 2.2-fold to 3.4-fold.

In rats, at day 1 and day 6, there were no changes in terms of AUC(0-24) and Cmax between 1 and 6 days. After 4 weeks of treatment female rats were more exposed than male rats. The apparent steady state exposure in terms of AUC(0-24) and Cmax increased from the low to the high dose less than dose-proportional in both sexes.

At day 28, Cmax and AUC (0-24) decreased compared to day 1. The diastereoisomeric ratio at steady state for AUC(0-24) was on average 0.4:0.6. The metabolite/parent ratio for AUC(0-24) was between 1.2 and 1.4 fold at day 6 and day 28, respectively.

In male dogs, no difference between day 1 and day 28 in terms of AUC and Cmax was seen. The diastereoisomeric ratio at steady state for AUC(0-24) on day 28 was 0.9:0.1. The metabolite/parent ratio for AUC(0-24) amounted dose-independently to 0.7. In plasma of dogs (S,R)-darolutamide prevailed with 9:1 whereas in humans the ratio was 1:6 under steady state conditions.

Distribution

Radio-HPLC analysis of plasma, human serum albumin, α1-acid glycoprotein and buffer incubated under the experimental conditions used for plasma protein binding and blood cell partitioning investigations demonstrated that [^{14}C]-ORM-15674 (darolutamide) was stable. Moreover, ORM-15674 and ORM-15341 (active metabolite) were stable in plasma from all species, human serum albumin and α1-acid glycoprotein.

There was little difference in binding of ORM-16497 ((S,R)-darolutamide) to the plasma proteins of rat, dog, monkey and human compared with binding of ORM-16555 ((S,S)-Darolutamide) in the same species.

Tissue distribution studies in mice and rats showed the same results in excretory organs, prostate and brain. In mice, darolutamide and keto-darolutamide and in rats total radioactivity exhibited low penetration into brain (brain/plasma ratio of AUC(0-24) < 0.05). Brain exposures to darolutamide in terms of AUC(0-24) were 4.5% of plasma exposure after single dose in rats and 1.9-3.9% after repeated dose in mice.

In rats, following oral administration, [^{14}C]-ODM-201 (1:1 mixture of the two diastereomers (S,R) and (S,S))-related material was absorbed and widely distributed. All investigated tissues contained quantifiable radioactivity 15 minutes after dose administration.

Absorption was relatively slow. Most tissues (65%) contained highest measured concentrations at 12 hours post-dose.

Elimination of drug-related radioactivity was rapid, with tissue concentrations in albino animals significantly lower at 24 hours than at 12 hours.

By 168 hours only the liver contained quantifiable radioactivity. Blood concentrations were approximately 60% of those in plasma suggesting ODM-201 had a higher affinity for the aqueous phase. In partially pigmented animals at 24, 72 and 168 hours, distribution was comparable to that seen in albino animals although concentrations in melanin containing tissues (pigmented skin and uveal tract/retina) were higher. Some evidence of limited/reversible binding to melanin containing tissues. Biliary secretion and renal clearance contributed to the elimination of [^{14}C]-ODM-201 and/or its radiolabelled metabolites. Only low levels of drug-related material penetrated the blood brain and the blood testes barriers.

In the prostate as target tissue with 0.45 a 10-fold higher tissue/plasma ratio of AUC(0-24) was observed compared to brain. No evidence of irreversible binding was observed.

Metabolism

In vitro

The primary human metabolic pathways (oxidation and glucuronidation) were well observed in rodent and dog hepatocytes. There was no unique human metabolite. The major differences between animal and human metabolism were:

- Metabolism in human hepatocytes was slower than metabolism in animals.

- The capacity to convert ORM-15341 (active metabolite) to ORM-16555 ((S,S)-Darolutamide) was higher in human than it was in rats and dogs.

- ORM-16497 ((S,R)-darolutamide)) was the predominant metabolite for dogs but for human the predominant metabolite was ORM-16555 ((S,S)-darolutamide).

In human liver hepatocytes, the main enzymes involved in the interconversion between the two diastereomers are CYP450, CBR, ADH, and AKR1C3.

In the human liver microsomes, ODM-201 inhibits weakly CYP2C9, CYP2C19 and CYP2D6 with an IC_{50}<100 µM. There was a slight tendency to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8 and CYP3A4 leading to an IC_{50}>100 µM. No inhibition was observed for CYP2E1.

In vivo

Keto-darolutamide was the only major circulating metabolite in mouse, rat, dog and human plasma. This metabolite had a similar pharmacological activity compared to darolutamide (and to both diastereomers). Exposure of darolutamide in terms of percentages AUC amounted to 49.9% in rats and to 28.6% in man. After repeated oral administration up to 28 days in males, the AUC ratio of keto-darolutamide/darolutamide in rats and dogs was 1.2 - 1.4 and 0.7, respectively. After multiple doses in humans, the systemic exposure to the metabolite was approximately 2-fold higher than that of darolutamide.

Excretion

In rats, radioactivity was excreted mainly via the biliary/faecal route after oral and intravenous administration of [^{14}C]darolutamide. Renal excretion contributed to the overall clearance of drug-related radioactivity by about 30% in intact rats.

In human, approximately 63% of the administered radioactivity is excreted into urine, another 32% of dose is excreted into the faeces (see clinical pharmacokinetics).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity study was submitted (see discussion on non-clinical aspects)

Repeat-dose toxicity

Dose Range Finding (DRF) studies in rats

In an initial 3-day DRF study, no mortality or clinical signs were observed up to the limit dose of 2000 mg/Kg in male rats. In a 7-day DRF oral study no signs of toxicity were reported up to 1000 mg/Kg. The last DRF study was conducted in rats treated during 14 days at the dose levels of 50, 200 or 800 mg/Kg/day. In this

study, signs of the pharmacodynamic activity were found in male rats (female phenotype of the mammary glands and secretory reduction in seminal vesicles) treated with darolutamide at the three dose levels.

4-week toxicity study in rats

Male and female rats were treated with darolutamide at 100, 300 or 1000 mg/Kg/day (10 M and 10 F) during 28 days. Treatment was tolerated in all groups, although some clinical findings were reported. As such, excess salivation was observed on the last week of treatment in animals receiving the highest dose level (1000 mg/Kg/day). In the case of male animals, they presented a dose-dependent decrease in body weight gain and lower food consumption at the three dose levels. At necropsy, prostate, epididymis and thymus were affected (table below).

Table 5: Main findings in the 28-day oral toxicity studies in rats with darolutamide

Darolutamide dose level (mg/kg/day)	Findings	Darolutamide $AUC_{(0-24)}$ (h×ng/mL)	keto-Darolutamide $AUC_{(0-24)}$ (h×ng/mL)
100	Prostate: weight ↓ (-63%) Epididymides: weight ↓ (-27%) Prostate & seminal vesicles: reduced secretion Thymus: weight ↑ (M) (+38%), inhibition of lymphocyte depletion consistent with natural involution (M)	88100 (M) 160000 (F)	104000 (M) 144000 (F)
300	Prostate: weight ↓ (-65%) Epididymides: weight ↓ (-32%) Prostate & seminal vesicles: reduced secretion Thymus: weight ↑ (M) (+33%), inhibition of lymphocyte depletion consistent with natural involution (M)	147000 (M) 216000 (F)	198000 (M) 209000 (F)
1000	Prostate: weight ↓ (-62%) Epididymides: weight ↓ (-28%) Prostate & seminal vesicles: reduced secretion Thymus: weight ↑ (M) (+31%), inhibition of lymphocyte depletion consistent with natural involution (M)	207000 (M) 242000 (F)	277000 (M) 248000 (F)

26-week toxicity study in rats

In this study, animals were treated at the same dose levels than the 4-week study, although they were twice daily administered with the aim of increasing the systemic exposure (2x50 (100), 2x150 (300), and 2x500 (1000) mg/kg/day). Treatment period was extended for 26 weeks. Two drug-free recovery groups, one from high dose and one from control were included to study the potential reversibility of symptoms during an additional four-week period of time. Some relevant findings were reported in all treated male groups, especially on male gonads. At necropsy, prostate, epididymis and testes were especially affected (table below). Minimal to slight atrophy of the mammary gland of male rats and minimal increase in vacuolation of the pars anterior of the pituitary gland was also present. No effects were reported in female animals. The original report of the study mentions a possible reduced activity clinically at 300 and 1000 mg/Kg/day in males and females. Given the findings observed in male animals, no no-observed-effect level (NOEL) was obtained. According to the study report, the NOAEL for female animals were 1000 mg/kg/day.

Table 6: Main findings in the 26-week oral toxicity studies in rats with darolutamide

Darolutamide dose level (mg/kg/day)	Findings	Darolutamide $AUC_{(0-24)}$ (h×ng/mL)	keto-Darolutamide $AUC_{(0-24)}$ (h×ng/mL)

100 (50x2)	Prostate: weight ↓ (-60%) Testes: weight ↓ (-13%) Prostate & seminal vesicles: atrophy Epididymides: weight ↓ (-30%), decrease in tubular diameter (10/10M) Pituitary gland: minimal increase in vacuolation of pars anterior (1/10 M) Mammary gland: minimal/slight atrophy (7/10 M)	66800 (M) 132000 (F)	73200 (M) 106000 (F)
300 (150x2)	Prostate: weight ↓ (-74%) Testes: weight ↓ (-17%) Prostate & seminal vesicles: atrophy Epididymides: weight ↓ (-38%), decrease in tubular diameter (10/10M) Pituitary gland: minimal increase in vacuolation of pars anterior (1/10 M) Mammary gland: minimal/slight atrophy (5/10 M)	105000 (M) 193000 (F)	114000 (M) 146000 (F)
1000 (500x2)	Prostate: weight ↓ (-76%) Testes: weight ↓ (-15%) Prostate & seminal vesicles: atrophy Epididymides: weight ↓ (-40%), decrease in tubular diameter (10/10M) Pituitary gland: minimal increase in vacuolation of pars anterior (2/10 M) Mammary gland: minimal/slight atrophy (6/9 M)	135000 (M) 292000 (F)	139000 (M) 253000 (F)

Repeat dose toxicity studies in non-rodents

DRF studies in dogs

An initial study consisting in an escalating dose phase (from 50 to 1000 mg/Kg/day for 3 days) and a confirmatory phase was performed (1000 mg/Kg/day for a week). A saturation of exposure was observed at 800 mg/Kg/day, so this dose level was selected for the 28-day repeated dose. In another DRF study conducted in dogs, escalating doses from 200 to 1000 mg/Kg/day were administered for two weeks. Dose level of 400 mg/Kg/day was well tolerated and selected for the 13-week study.

4-week toxicity study in dogs

Animals received darolutamide at the dose levels of 50, 200 or 800 mg/Kg/day. After four weeks of treatment, a slight body weight loss associated with lower food consumption was observed. At necropsy, lower prostate weights, diffuse atrophy in prostate, oligospermia and vacuolation of the epididymal epithelium (table below) were reported.

Table 7: Main findings in the 4-week oral toxicity studies in dogs with darolutamide

Darolutamide dose level (mg/kg/day)	Findings	Darolutamide $AUC_{(0-24)}$ (h×ng/mL)	keto-Darolutamide $AUC_{(0-24)}$ (h×ng/mL)
50	Prostate: weight ↓ (-78%), atrophy Epididymis: weight ↓ (-24%), oligospermia and vacuolation of epithelium	71000	51200
200	Prostate: weight ↓ (-82%), atrophy Epididymides: weight ↓ (-36%), oligospermia and vacuolation of epithelium	157000	104000
800	Prostate weight ↓ (-79%), atrophy Epididymides: weight ↓ (-32%), oligospermia and vacuolation of epithelium	162000	107000

13-week toxicity study in dogs

In this study, the maximum dose level was 2x200mg/Kg/day, given that no increase in exposure was observed at higher dose levels. A slight mean body weight loss in females and white-coloured faeces indicating the presence of darolutamide in faeces were reported at 400 mg/Kg/day. At necropsy, prostatic atrophy, lower weight of epididymides and decreased tubular diameter and epithelial atrophy were found (table below). These findings were reported as reversible, as they were minimal at the end of the 4-week recovery period.

Table 8: Main findings in the 13-week oral toxicity studies in dogs with darolutamide

Darolutamide dose level (mg/kg/day)	Findings	Darolutamide $AUC_{(0-24)}$ (h×ng/mL)	keto-Darolutamide $AUC_{(0-24)}$ (h×ng/mL)
50 (25x2)	Prostate: weight ↓ (-67%), atrophy Epididymides: weight ↓ (-33%), decreased tubular diameter, epithelial atrophy	85800 (M) 92400 (F)	80300 (M) 67800 (F)
150 (75x2)	Prostate: weight ↓ (-62%), atrophy Epididymides: weight ↓ (-11%), decreased tubular diameter, epithelial atrophy	115000 (M) 120000 (F)	79400 (M) 123000 (F)
400 (200x2)	Prostate: weight ↓ (-71%), atrophy Epididymides: weight ↓ (-36%), decreased tubular diameter, epithelial atrophy	116000 (M) 166000 (F)	96300 (M) 123000 (F)

39-week toxicity study in dogs

Dose levels were the same than those used in the 13-week repeated dose toxicity study, i.e. 2x25, 75x2, 200x2 mg/Kg/day. Recovery groups were added to the study, which were maintained during an 8-week treatment-free period. A lower slight mean body weight gain was observed. Slight decreases in mean red blood cell parameters in males of the medium and high dose levels were reported from weeks 13 to 39. At necropsy, the prostate and epididymis weight were lower than control with histological correlation (table below). Minimal or slight tubular dilatation and tubular degeneration/atrophy was reported with increased testis weight.

Table 9: Main findings in the 39-week oral toxicity studies in dogs with darolutamide

Darolutamide dose level (mg/kg/day)	Findings	Darolutamide $AUC_{(0-24)}$ (h×ng/mL)	keto-Darolutamide $AUC_{(0-24)}$ (h×ng/mL)
50 (25x2)	Prostate: weight ↓ (-79%), atrophy Epididymides: weight ↓ (-31%), decreased tubular diameter, epithelial atrophy and reduced sperm content Testes: weight ↑ (+10%), minimal tubular dilatation (1/4 M)	96700 (M) 78100 (F)	72600 (M) 58400 (F)
150 (75x2)	Prostate: weight ↓ (-80%), atrophy Epididymides: weight ↓ (-26%), decreased tubular diameter, epithelial atrophy and reduced sperm content Testes: weight ↑ (+16%), sperm accumulation (1/4 M)	103000 (M) 145000 (F)	75200 (M) 135000 (F)
400 (200x2)	Prostate: weight ↓ (-83%), atrophy Epididymides: weight ↓ (-30%), decreased tubular diameter, epithelial atrophy and reduced sperm content Testes: weight ↑ (+23%), tubular luminal dilatation and tubular degeneration/atrophy (4/4 M), tubular luminal sperm accumulation with granulomatous inflammation (2/4 M)	206000 (M) 217000 (F)	152000 (M) 166000 (F)

Genotoxicity

The genotoxicity of darolutamide was studied in three GLP tests.

Salmonella/microsome test (Ames): bacterial mutagenicity assay was performed with darolutamide. Two independent studies, in five Salmonella typhimurium strains up to 5000 µg/plate (R-9724), in the absence and presence of metabolic activation (rat liver S9 mix) were performed. Signs of toxicity to test bacteria and precipitation of darolutamide were observed at dose levels of 2500-5000 µg/plate. No evidence of mutagenic activity was seen in this study.

In vitro mammalian cell test: the chromosome aberrations assay in cultured peripheral human lymphocytes was conducted with darolutamide in five independent studies. The induction of chromosome aberrations was reported in the presence and absence of metabolic activation (S9 fraction) at concentrations ≥200 µg/mL and ≥240 µg/mL, respectively. These concentrations were non-toxic and the results exceeded the historical control data. Darolutamide was positive in this test.

Combined micronucleus test and Comet assay in the rat: in vivo genotoxicity tests with darolutamide consisted in micronucleus test and Comet assay test in rats. In the micronucleus test, no difference in the frequency of micronucleated PCEs was observed in the three dose levels tested (100, 500 and 1000 mg/Kg) and the control group. In the Comet assay, no DNA damage was observed in the animals received darolutamide.

Carcinogenicity

No carcinogenicity studies were submitted (see discussion on non-clinical aspects).

Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were submitted (see discussion on non-clinical aspects).

Effects on reproductive organs were seen in the 14-day, 28-day and 13-week rat study and in the 7-day, 28-day, 13-week and 39-week dog study. In the 14-day rat study reduction of prostate and epididymis weight, necropsy of the small seminal vesicles, secretory reduction and female phenotype of the mammary glands were observed for all doses. In the 28-day rat study, reduction of prostate and epididymis weight and reduction of prostatic secretory were observed at all doses.

In the 26-week rat study, reduction of prostate, testes and epididymis weight, prostate, seminal vesicle and mammary gland atrophy and a diameter reduction of epididymal tubules.

In the 7-day dog study, decreased prostate weight at a diffuse atrophy in the prostate at 1000mg/kg/day.

In the 28-day dog study, decreased of the prostate and epididymis weight, reduction of oligospermia in the epididymis and a reduction of the vacuolization of the epididymal epithelium in the epididymis at all doses.

In the 13-week dog study, decreased prostate and epididymis weight and increased testes weight were observed at all doses. At the end of the recovery period there was still a reduction of prostate weight, a minimal prostate atrophy and decreased tubular diameter of the epididymis.

In the 39-week dog study, decreased prostate and epididymis weight and increased testes weight, prostatic and epididymal atrophy, changes in the tubular diameter of epididymis, epithelial atrophy and reduced sperm content were observed at all doses. Minimal testicular Leydig cell hypertrophy was observed at 2x75 and 2x200 mg/kg/day. All these symptoms were reversible except the prostate weight.

Toxicokinetics

All references to the exposure margins compared to humans are based on the mean human 1200 mg/kg/day (2x600 mg/kg/day), exposure data: AUC(0-24h) of darolutamide of 57.6 hxµg/mL and Cmax of Darolutamide of 3.33 µg/mL.

The metabolite/parent drug ratio after repeated dose in rats is 1.2.-1.4 and 0.7 in dogs which means that rats were more exposed to the metabolite compound and dogs were more exposed to the parent compound.

Rats exposure to the diastereomers were relatively the same between (S,R) and (S,S)-darolutamide whereas the dogs were exposed mostly to (S,R)-Darolutamide (around 90%).

Local tolerance

The intended route of administration is oral. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies in Wistar rats. No indication of local adverse reactions related to the drug. No dedicated local tolerance testing was provided (see discussion on non-clinical aspects).

Other toxicity studies

Phototoxicity

Both darolutamide and keto-darolutamide absorb light in the UVB range from 290 to 320 nm with the highest absorption at 290 nm. The calculated molar absorption coefficients were 23100 and 22500 L mol-1 cm-1, respectively, exceeding the proposed threshold of 1000 L mol-1 cm-1 according to the ICH S10 guideline.

The results from the in vitro 3T3 assay, utilizing promethazine hydrochloride as a positive control, indicated that darolutamide is not phototoxic.

2.3.5. Ecotoxicity/environmental risk assessment

Table 10: Summary of main study results

Substance (INN/Invented Name): darolutamide			
CAS-number (if available): 1297538-32-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.41	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	6.0	µg/L	> 0.01 threshold (Y)
PEC $_{surfacewater}$ refined (prevalence in UK 2013)	1.0	µg/L	> 0.01 threshold (N)

Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*log*K_{oc} = 2.61-3.33			K_{oc}<10000
Water solubility	OECD 105	12.9 mg/L (25ºC, pH 7)			
Dissociation constant	OECD 112	Neutral			
Hydrolysis	OECD 111	Stable at pH 4, 7, and 9			
Vapour Pressure	OECD 104	2.61 x 10^{-5} Pa (20ºC)			
Ready Biodegradability Test	OECD 301	Not degraded on day 29			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} 35.8-134.9 days (both sediments)			One metabolite detected
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species* (72 h)	OECD 201	NOEC LOEC	≥8,037 >8,037	µg/L	Algal (*Desmodesmus subspicatus*)
Daphnia sp. Reproduction Test	OECD 211	NOEC LOEC	≥1,137 >1,137	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 240 (with modifications)	NOEC LOEC	28 89	µg/L	Fish (fathead minnow, *Pimephales promelas*) life-cycle
Activated Sludge, Respiration Inhibition Test (3 h)	OECD 209	NOEC LOEC	≥12,900 >12,900	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	128.16	mg/kg	Chironomide (*Chironomus riparius*)

Darolutamide is not a PBT substance.

Considering the above data, darolutamide should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

The results of the Fish Multi Generation Life-Cycle test with Pimephales promelas was questioned. A high variability of spawning between the control replicates was reported and excluding one replicate as an outliner from the statistical evaluation was discussed. This would have resulted in an Risk Quotient above 1. Due to the methodological issue of excluding one replicate and the fact that non-spawning fish in fathead minnow (Pimephales promelas) in laboratory studies are part of the natural variation, additional data are required to conclude on the potential risk of darolutamide to the aquatic environment. As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of darolutamide to the environment.

The applicant commits to perform the following studies as follow-up measures: a fish study following the OECD 229 guideline.

2.3.6. Discussion on non-clinical aspects

The non-clinical data package for darolutamide has been conducted in line with ICH M3 and S9 guidelines.

In vitro, darolutamide exhibited low nanomolar potency inhibition against rat androgen receptor, which was similar with the inhibitory activity observed with bicalutamide. Darolutamide, its diastereomers and metabolite were potent and full hAR antagonists (more effective than bicalutamide). Moreover, bicalutamide showed an agonistic activity at concentrations above 100 nM, whereas darolutamide did not have an agonistic activity up to 3 µM. The two diastereomers and the metabolite showed a modest agonistic activity in HEK293 cells (65 nM).

The agonistic activity was also measured by the capacity to induce an AR nuclear translocation. Bicalutamide was 25-times more potent than darolutamide and 5-times more potent than ORM-15341 (active metabolite) in inducing AR nuclear localization. Both compounds also inhibited testosterone-induced nuclear translocation of AR better than bicalutamide. Additional *in vitro* binding studies revealed darolutamide and its metabolite as antagonists in W742L, F877L and T878A mutations of the AR whereas, bicalutamide showed an agonistic activity against W741L mutant and enzalutamide and apalutamide showed an agonistic activity against F876L mutant. Although AR binding was shown in cellular systems, no information related to the potential genes transcription after darolutamide treatment, including PSA, was reported. The applicant submitted the results from a set of studies (Sugawara et al 2019), in which darolutamide reduced the gene expression of androgen target gene expression, such as KLK3 and FKBP5. Moreover, the racemate, the (S,R) and (S,S) forms of darolutamide were shown to behave similarly in several cellular assays (prostate cancer cells lines, AR activity, AR wild-type and mutant dimerization). The capacity of darolutamide and its metabolite to inhibit the prostate cancer cell growth was better than bicalutamide (100% inhibition vs 65%). Overall, all three substances (darolutamide, (S,R) darolutamide and (S,S) darolutamide) show similar pharmacological activity *in vitro*.

In vivo, darolutamide showed an antagonistic activity on rAR with a decrease of the relative mass of the prostate and seminal vesicles in the immature rats. This decrease was observed even at the low concentration and was dose-dependent. An experiment was made to test the tumour re-growth after a first tumour growth suppressed by orchidectomy with a castration resistant prostate cancer in mice xenograft model. Darolutamide induced a xenograft tumour regression (50mg/kg darolutamide for 37 days) compared to untreated castrated mice and, the effect was higher at twice daily than once daily.

The effect of darolutamide was tested on the growth of Vertebral-Cancer of the Prostate (VCaP) tumours in nude intact or castrated mice. The result was compared with enzalutamide, used as a reference compound. The anti-tumour activity in these studies was not compared with any other first or second-generation antiandrogen therapy. In both experiments, no change in the tumour weight was observed but a decrease on the serum PSA level was observed. For the castrated mice, a dose-dependent trend of inhibition of the tumour growth was observed.

No *in vivo* pharmacology studies conducted with diastereomers were provided. However, as the two diastereomers (S,S)-darolutamide and (S,R)-darolutamide rapidly interconvert enzymatically *in vivo*, the use of a mixture of the two diastereomers in the final drug product ODM-201 (1:1 mixture of the two diastereomers (S,R) and (S,S)) is considered acceptable.

In view of the secondary pharmacodynamics data provided, side effects like tiredness, sexual dysfunction, neurological disorders and seizure can be expected but at low risk because the brain distribution of darolutamide is low. Preclinical studies in rodents have demonstrated low blood-brain barrier penetration of darolutamide with a brain/plasma ratio <0.05. This may portend less CNS-related side effects in humans, as compared to available therapies, which showed an about 10-fold higher brain/plasma ratio.

A specific study was conducted on GABAa receptor. Enzalutamide and apalutamide are well known to induce seizures by an antagonistic activity on GABAa receptor. Darolutamide and its metabolite seem less potent to

induce seizures because their IC50 for GABAa inhibition were higher than the one for enzalutamide and the brain distribution of darolutamide was weak. Moreover, no seizure was observed *in vivo* in animals.

Gastrointestinal tract was identified as a potential off target for darolutamide. Rats administered with darolutamide showed delayed gastric emptying and intestinal transit at 30 mg/Kg of darolutamide, which was attributed to the activity on receptor GABAA which is found in the myenteric neurons, being a modulator of motor and secretory GI activity. A review for the potential actions of darolutamide on GABA receptors, hPR and serotonin transporters was submitted. The correspondent margin of exposure was also estimated after comparison of IC50 values for each receptor with therapeutic human free Cmax. The review concluded that exposure obtained after darolutamide administration is slightly below the concentration requested to exert an effect on the analysed receptors. Thus, darolutamide is unlikely to produce an effect on the gastrointestinal tract, although it cannot be ruled out.

In terms of cardiovascular safety assessment, darolutamide weakly inhibited *in vitro* the hERG current and dose-dependently inhibited the L-type calcium channel. *In vivo*, in anaesthetised dogs, darolutamide slightly decreased the QT interval duration, but this effect was not found in conscious dogs. (see SmPC section 5.3). QT/QTc shortening and AV block exhibited in the anaesthetized dog study was attributed by the applicant to anaesthesia effects. It was noted that the two *in vitro* studies were not conducted in compliance with GLP standard. Furthermore, there was no control group and no analysis related to the effect of the metabolite and one of the diastereomers in the non-conscious dog study. Also, no study with (S,S) diastereomer in conscious dogs was provided when anaesthesia was considered to justify the observed AV-block. Considering these limitations and the available results from safety pharmacology and toxicology studies, the risk for QT prolongation cannot be excluded in clinic and adequate measures have been included in the SmPC (see also discussion clinical safety).

With regards to the CNS and respiratory system, darolutamide was well tolerated up to the highest dose of 1000 mg/kg/day in the corresponding studies in rats. No physiologically relevant acute effects on CNS and respiratory function were seen. Furthermore, no clear treatment-related neurobehavioral abnormalities were noted although a slight trend for reduced motor activity was observed in both sexes at ≥300 mg/kg/day in week 3. This was accompanied by a reduced alertness in males. No significant alteration in motor activity or behaviour were observed in the 4-week repeat dose study in rats. The absence of follow-up and supplemental studies in CNS do not permit to conclude a definitive effect of darolutamide on the CNS system from a non-clinical point of view. However, clinical data indicated no increase in cognitive and memory issues.

In terms of pharmacokinetics, the qualitative metabolite profiles of darolutamide in rats as well as the overall biotransformation pathways seem to be quite comparable to the profiles obtained in human plasma. However, the metabolite profiles of darolutamide between dogs and human are different. The dogs are more exposed to darolutamide whereas humans are more exposed to keto-darolutamide. As darolutamide and keto-darolutamide have the same pharmacologic activity this metabolite profile difference is not a relevant problem.

Despite differences between species in the ratio of diastereomers (S,R)-darolutamide to (S,S)-darolutamide, the available results clearly showed interconversion of diastereomers *in vivo*.

The safety profile of darolutamide was characterised in rats and dogs through the conduct of repeat-dose toxicity studies of up to 6- and 9-month, toxicokinetic data, genotoxicity and phototoxicity studies. No single dose toxicity study was conducted which is acceptable in line with Guideline ICH S9.

According to the pre-clinical data and consistent with the pharmacologic activity, the primary target organ was the reproductive system. In repeated dose toxicity studies in rats and dogs, the main findings were changes in the male reproductive organs (decreases in organ weight with atrophy of the prostate and epididymides). These

effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy and secretory reduction in seminal vesicles and mammary glands in rats as well as testicular hypospermia, seminiferous tubule dilatation and degeneration in dogs. Changes in the male reproductive organs in both species were consistent with the pharmacological activity of darolutamide and reversed or partially resolved after 4- to 8-week recovery periods (see SmPC section 4.8). No others adverse effects were observed. No deaths occurred during the treatment period. The relevance of the dog study was questioned considering that dogs were mostly exposed to (S,R)-Darolutamide (around 90%) while humans are mostly exposed to (S,S)-darolutamide. The exposure multiple to (S,S)-Darolutamide in dogs compared to humans is very low, with a maximum exposure multiple as low as 0.3 (AUC0_24h). However, the safety assessment of the diastereomers is considered adequate considering the similar activity of the diastereomers, the *in vivo* enzymatic interconversion, the total exposure of both stereoisomers, and the 3Rs policy.

Long term animal studies to evaluate the carcinogenic potential of darolutamide have not been submitted. From a clinical point of view, the median overall survival for this condition is 4 years, with a substantial number of patients that will survive beyond this point and thus could be at risk of secondary tumours due to treatment. Therefore, the claimed indication cannot be considered as advanced cancer and a non-clinical approach following the ICHS9 guideline is not endorsed. The applicant has been asked to justify the absence of carcinogenesis studies for darolutamide with solid proofs of any carcinogenic effects during the non-clinical toxicity studies (weight-of-evidence) and, possibly, publicly available information on carcinogenic potential of other drugs of the same class. The applicant was asked to elaborate on the possible reasons for a different non-clinical safety profile between darolutamide and the already approved non-steroidal antiandrogens (apalutamide and enzalutamide) which are subject to carcinogenicity studies. Whereas proliferative events (hypertrophy) was observed in the repeated-dose toxicity package for apalutamide, no proliferative events were observed in non-clinical studies for darolutamide. The results of the 2-year carcinogenicity study for apalutamide are not yet available. Enzalutamide 2-year carcinogenicity study showed urothelium papilloma and carcinoma of urinary bladder that could be potentially related to calculi and crystals. Other tumours were observed, potentially related to the primary pharmacology. It included fibroadenoma of mammary glands and benign thymoma of thymus in males, benign granulosa cell tumours of ovaries in females, and adenoma of pituitary pars distalis in both sexes. In the absence of relevant data to adequately assess the carcinogenicity potential of darolutamide, the applicant will submit results of a 6-month Tg-rasH2 mouse study (see RMP).

No antigenicity, immunotoxicity, dependence, metabolites, impurities studies were submitted which is considered acceptable for this compound. Darolutamide belongs to a class of products with a documented absence of dependence potential. Moreover, no dependence effects were observed in the toxicology study *in vivo*. With regards to the metabolites, keto-darolutamide was the major metabolite in all animal species and its pharmacological activity was similar to darolutamide.

No pharmacodynamic drug interactions studies were submitted which was considered acceptable as darolutamide is not administered as a combination therapy with other anti-tumour drugs.

Darolutamide is considered as a non-phototoxic compound based on available data. Rash (mostly maculo-papular) were observed in the clinical studies but did not seem to be drug-related.

Studies on reproductive toxicity have not been submitted which was considered in line with the recommendations of the ICH S9 guideline. However, male fertility is likely to be impaired based on the findings in repeat-dose toxicology studies in rats and dogs, which are consistent with the pharmacological activity of darolutamide as discussed above (see SmPC section 5.3). It is not known whether darolutamide or its metabolites are present in semen. In human, darolutamide half-life was around 5 days in the worst case. If the

patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method (<1% failure rate per year) should be used during and for 1 week after completion of treatment with darolutamide to prevent pregnancy (see SmPC sections 4.4 and 4.6).

Nubeqa is not indicated in women of childbearing potential. It is not to be used in women who are, or may be, pregnant or breast-feeding (see SmPC sections 4.1 and 4.3). Based on its mechanism of action, darolutamide may cause foetal harm. Exposure of the foetus to an androgen receptor inhibitor through seminal transfer to the pregnant woman has to be avoided, as this could affect development of the foetus. Therefore, darolutamide is contraindicated in women who are or may become pregnant (see SmPC sections 4.3 and 4.6).

It is also unknown whether darolutamide or its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of darolutamide or its metabolites into milk (see SmPC section 5.3). A risk to the breast-fed child cannot be excluded.

With regards to fertility, animal studies showed that darolutamide affected the reproductive system in male rats and dogs (see above and SmPC section 5.3). There are no human data on the effect of darolutamide on fertility. Based on animal studies, Nubeqa may impair fertility in males of reproductive potential (see SmPC section 4.6).

Regarding genotoxicity, darolutamide did not induce mutations in the microbial mutagenesis (Ames) assay. At high concentrations, darolutamide did induce structural chromosome aberrations *in vitro* in cultured human lymphocytes. However, in the *in vivo* combined bone marrow micronucleus test and the Comet assay in the liver and duodenum of the rat, no genotoxicity was observed at exposures in excess of the maximum human exposure. The genotoxicity effects were observed at exposure in excess of the maximum human exposure (see SmPC section 5.3), indicating little relevance to clinical use.

Concerning the Environmental risk assessment, the logKow value of darolutamide was below 4.5. Consequently, this substance cannot be identified as a persistent, bioaccumulative and toxic (PBT) substance. Since the Phase I PECsw of Darolutamide (6µg/L) exceed the action limit of 0.01µg/L, and that it is a hormonal drug, darolutamide was further assessed in environmental fate and ecotoxicological effects studies. A Phase II environmental fate and effects assessment was performed according to EMA Guideline. The available data do not allow to conclude definitively on the potential risk of darolutamide to the aquatic environment, especially to fish. The applicant is recommended to perform a fish study following the OECD 229 guideline.

2.3.7. Conclusion on the non-clinical aspects

Darolutamide development has been performed in line with ICH S9 guideline. All important non-clinical safety findings which have been identified during development have been adequately addressed.

The CHMP considers the following measures necessary to address the non-clinical issues:

The applicant should provide the results of the 6-month Tg-rasH2 mouse carcinogenicity study by 30 June 2022 (see RMP).

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

Table 11: Overview of darolutamide clinical studies

Clinical phase	Bayer study no / Study name (Orion study no)	Countries/regions	Study period	Study design	Primary and secondary objectives	Study population	Treated patients / exposed subjects as of 03SEP2018	Treatment and dose
5.3.1 Reports of Biopharmaceutic Studies - 5.3.1.1 Bioavailability (BA) Study Reports								
Phase 1	17830 ARAFOR (3104003)	Finland, France and Latvia	FPFV 14MAR2013 Report cut-off 30APR2017 (6 patients ongoing with treatment)	Open-label, randomized, uncontrolled, multicenter, 2-component (PK and extension)	Primary: PK Component: Relative bioavailability of 2 tablet products compared to the capsule; the effect of food on the PK of tablet products; short term safety and tolerability Extension Component: Long-term safety and tolerability	Patients with mCRPC	30 3 patients ongoing with treatment	Darolutamide 600 mg PK Component: single dose orally with and w/o food Extension Component: multiple dose b.i.d. orally Concurrently with ADT (both components)
5.3.3 Reports of Human Pharmacokinetic (PK) Studies - 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports								
Phase 1	17831 ARIADME (3104005)	UK	FSFV 26MAR2015 LSLV 20MAY2015	Open-label, non-randomized, 2-part, single center	Primary: Part 1: Absolute bioavailability Part 2: Mass balance and routes of excretion of total radioactivity after a single oral 300 mg dose of ^{14}C-darolutamide given as a solution	Healthy volunteers	Total: 12 Part 1: 6 Part 2: 6	Part 1: darolutamide 300 mg single oral tablet followed by single IV microtracer dose (not to exceed 100 µg) of ^{14}C-darolutamide Part 2: 300 mg single oral solution of ^{14}C-darolutamide

5.3.3 Reports of Human Pharmacokinetic (PK) Studies - 5.3.3.2 Patient PK and Initial Tolerability Study Reports								
Phase 1	17719	Japan	FPFV 23FEB2015 LPLV 21DEC2017	Open-label, non-randomized, uncontrolled, single center, dose-escalation	Primary: Safety and tolerability; PK of darolutamide and its major metabolite.	Japanese patients with mCRPC	9	Darolutamide 300 mg 600 mg Single (with and w/o food) and multiple (with food) dose b.i.d. orally Concurrently with ADT
Phase 1/2	17829 ARADES (3104001)	Czech Republic, Estonia, Finland, France, UK, US	FPFV 28MAR2011 LPLV 09JUL2013	Phase 1: Open-label, non-randomized, uncontrolled, multicenter, first in man, dose-escalation Phase 2: Open-label, randomized, uncontrolled, multicenter	Primary: Phase 1: Safety and tolerability, including DLTs and MTD Phase 2: Efficacy and safety of at 3 dose levels Secondary: Phase 1: PK profile of darolutamide and its major metabolite after single and multiple dose administrations in fed condition at different dose levels Both Phases: preliminary antitumor activity; the dose(s) for further clinical studies	Patients with mCRPC	Total: 134 Phase 1: 24 Phase 2: 110	Phase 1: Darolutamide 100-900 mg b.i.d. orally with food Phase 2: Darolutamide 100 mg 200 mg 700 mg b.i.d. orally with food Concurrently with ADT (both phases)
5.3.3 Reports of Human Pharmacokinetic (PK) Studies - 5.3.3.3 Intrinsic Factor PK Study Reports								
Phase 1	17721	Germany	FSFV 13SEP2016 LSLV 10APR2017	Open-label, non-randomized, single-dose	Primary: Potential effect of hepatic or renal impairment on PK of darolutamide. Secondary: Potential effect of hepatic or renal impairment on PK of the diastereomers of darolutamide and the major metabolite; safety and tolerability	Healthy volunteers Subjects with moderate HI Subjects with severe RI	Total: 29 10 healthy volunteers, 9 subjects with moderate HI, 10 subjects with severe RI	Darolutamide 600 mg single dose orally
5.3.3 Reports of Human Pharmacokinetic (PK) Studies - 5.3.3.4 Extrinsic Factor PK Study Reports								
Phase 1	17723	Germany	FSFV 09FEB2016 LSLV 11MAY2016	Open-label, non-randomized, fixed-sequence, single center	Primary: Potential perpetrator effect of darolutamide on rosuvastatin PK Secondary: PK profiles of single and multiple dose darolutamide and of its main metabolite and diastereomers in healthy male and postmenopausal female subjects; safety; effect of gender on the PK of darolutamide	Healthy volunteers	30	Period 1: rosuvastatin alone Period 2: darolutamide 600 mg single dose on Day 1, followed by 600 mg b.i.d. for 5 days (Days 4-8) with single dose rosuvastatin on Day 8
Phase 1	17726	Germany	FSFV 15FEB2017 LSLV 04MAY2017	Open-label, non-randomized, fixed-sequence, single center	Primary: The effect of itraconazole, a strong CYP3A4 inhibitor, on the PK of darolutamide, its diastereomers and major metabolite; the effect of rifampicin, a strong CYP3A4 inducer, on the PK of darolutamide, its diastereomers and major metabolite Secondary: Safety and tolerability	Healthy volunteers	15	Darolutamide 600 mg, 3 single doses orally Period 1: alone Period 2: with multiple doses of itraconazole Period 3: with multiple doses of rifampicin
Phase 1	18860	Germany	FSFV 02AUG2017 LSLV 26OCT2017	Open-label, non-randomized, fixed-sequence, single center	Primary: The effect of darolutamide on the PK of MDZ and non-conjugated dabigatran Secondary: the effect of darolutamide on the PK of 1-OH midazolam and total dabigatran; safety and tolerability	Healthy volunteers	15	Period 1: DABE and MDZ alone Period 2: darolutamide 600 mg b.i.d. for 11 days (with DABE on Day 3 and Day 9 and MDZ on Day 9)

5.3.5 Reports of Efficacy and Safety Studies - 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
Phase 3	17712 ARAMIS (3104007)	Argentina, Austria, Australia, Belarus, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, UK, US	FPFV 12SEP2014 Primary completion 03 SEP 2018	Randomized, double-blind, placebo-controlled	Primary: Superiority of darolutamide + ADT over placebo + ADT in MFS Secondary: Benefit of darolutamide for OS, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, time to first SSE; safety and tolerability	Patients with CRPC who have undetectable metastases by conventional imaging techniques (i.e. CT, MRI, BS)	Darolutamide: 954 Placebo: 554 Ongoing with treatment: Darolutamide: 615 Placebo: 200	Darolutamide 600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a daily dose of 1200 mg, or placebo Concurrently with ADT
5.3.5 Reports of Efficacy and Safety Studies - 5.3.5.2 Study Reports of Uncontrolled Clinical Studies								
Phase 2	18035 ARADES-EXT (3104002)	Czech Republic, Estonia, Finland, France, UK, US	FPFV 30JUN2011 LPLV 21OCT2015	Extension study for study 17829	Primary: Long-term safety and tolerability Secondary: Antitumor activity	Patients with mCRPC	76 patients from study 17829 continued to extension from Phase 1: 19 from Phase 2: 57	Same dose as given in week 12 of study 17829. One dose escalation at time of disease progression was allowed.

5.3.5 Reports of Efficacy and Safety Studies - 5.3.5.4 Other Study Reports and Related Information								
Phase 3	17777 ARASENS	Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, China, Finland, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Sweden, Taiwan, UK, US	FPFV 30NOV2016 Enrollment completed, primary completion not reached	Randomized, double-blind, placebo-controlled	Primary: Superiority of darolutamide in addition to standard ADT and docetaxel over placebo in addition to standard ADT and docetaxel in OS. Secondary Time to CRPC, time to initiation of subsequent antineoplastic therapy, SSE–FS, time to first SSE), time to initiation of opioid use for ≥7 consecutive days, time to pain progression, time to worsening of physical symptoms of disease (QoL), safety	Patients with mHSPC	1303 darolutamide or placebo (estimated number of darolutamide-treated patients: 650) 1071 patients ongoing with treatment	Darolutamide 600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a daily dose of 1200 mg, or placebo Concurrently with ADT 6 cycles of docetaxel at 75 mg/m^2

2.4.2. Pharmacokinetics

Introduction

Darolutamide is poorly soluble in aqueous solvents over a large pH range and generally more soluble in organic solvents (see SmPC section 5.2). It is a Biopharmaceutics Classification System (BCS) Class 2 compound (low solubility, high permeability). The final drug product is a 300 mg film-coated tablet (see quality aspects). Besides the proposed tablet, a 100 mg powder-in-capsule was developed and used in early Phase ½ clinical trials, and minor variants of the proposed tablet were also developed. The tested drug products forms were bridged with the final drug product for commercial use by a bioequivalence study. The recommended dose is 600 mg (2 x 300 mg tablet) twice daily (b.i.d.), equal to a total daily dose of 1200 mg. Darolutamide has been studied in patients with metastatic CRPC (mCRPC) in Phase 1 and Phase 2 studies, and in patients with non-metastatic CRPC (nmCRPC) in a Phase 3 study (see Table 18).

Table 12: Table of clinical studies presented for darolutamide PK characterisation

Study no. Bayer/ [Orion] Region Location of study report	Study Objectives	Study Design	Dose of darolutamide (Concurrently with ADT)[a]	Study population / number of treated patients (as of 03 SEP 2018)
Dose Escalation and Expansion				
17829 [3104001] **ARADES** Europe, US Module 5.3.3.2, Report R-9584 Exploratory biomarker Module 5.3.5.4, Report R-12659	**Phase 1**: PK, Safety and tolerability, including DLTs and MTD **Phase 2**: Efficacy and safety at 3 dose levels Exploratory objective: bone biomarkers	First in man **Phase 1**: Open-label, non-randomized, uncontrolled, first-in-man, dose-escalation **Phase 2**: Open-label, randomized, multicenter	**Phase 1**: multiple dose of 100 – 900 mg b.i.d. orally with food **Phase 2**: multiple dose of 100 mg, 200 mg, and 700 mg b.i.d. orally with food	Men ages 55 - 83 years with mCRPC / **134 total** Phase 1: 24 Phase 2: 110
Bioavailability and Metabolism				
17831 [3104005] **ARIADME** United Kingdom Module 5.3.3.1, Report R-11003 Module 5.3.3.1, Report PH-40075	Absolute bioavailability, mass balance, PK and biotransformation	**Phase 1** Open-label, non-randomized, 2 part, single center, single dose	**Part 1**: 300 mg single oral tablet w/o food followed by single i.v. microtracer dose (not to exceed 100 µg) of ^{14}C-darolutamide **Part 2**: 300 mg single oral solution of ^{14}C-darolutamide	Healthy male volunteers Ages 50 to 65 years **12** total Part 1: 6 Part 2: 6
Bioavailability and PK				
17830 [3104003] **ARAFOR** Europe Module 5.3.1.1, Report R-9789	**PK Component**: bioavailability, food effect; capsule and 2 different tablet formulations **Extension Component**: long-term safety and tolerability	**Phase 1** Open-label, randomized, uncontrolled, multicenter, 2 component (PK and extension)	**PK component**: Single dose of 600 mg orally with and w/o food. **Extension component**: multiple dose of 600 mg orally b.i.d with food	Men ages 54 - 86 years with chemotherapy naïve mCRPC **30 total** (15 patients per tablet formulation)
17719 Japan Module 5.3.3.2, Report PH-39192 Module 5.3.3.2, Report Addendum PH-40296	Single dose: PK and food effect Multiple dose: safety, tolerability, PK	**Phase 1** Open-label, non-randomized, single-center uncontrolled, 2 component (PK and safety and tolerability)	Single dose (with and w/o food) 300 mg or 600 mg orally; and multiple dose (with food) 300 mg or 600 mg orally b.i.d.	Japanese men Ages 64 - 83 years with mCRPC **9 total** Cohort 1: 3 (300 mg) Cohort 2: 6 (600 mg)
Phase 3 with PK component				
17712 [3104007] **ARAMIS** North America, Asia Pacific, ROW[b] Module 5.3.5.1, Report PH-39723	Efficacy and safety compared to placebo Pivotal study	**Phase 3** Randomized, double-blind, placebo-controlled	600 mg b.i.d. orally with food	Men ages 50 - 92 years with nmCRPC[c] Darolutamide: **954 total** Placebo: **554 total**
Bioavailability and Metabolism Special Populations – Hepatic or Renal Impairment				
17721 Germany Module 5.3.3.3 Report PH-39976	Evaluate darolutamide in renally and hepatically impaired subjects	**Phase 1** Open-label, non-randomized, single dose.	600 mg darolutamide (single dose) Dosing with food.	Non-cancer male volunteers **29 total** Ages 52 to 78 years Healthy (10) Moderate HI (9) Severe RI (10)

Bioanalytical method

The two diastereomers (S,R)-darolutamide and (S,S)-darolutamide and the main active metabolite, keto-darolutamide were quantified by LC-MS/MS in human plasma. The validation of these methods met the acceptance criteria. The two parent diastereomers were also quantified with LC-MS/MS in urine samples. This method was adequately qualified in urine.

Pharmacokinetic data analysis

The clinical pharmacokinetics of darolutamide was analysed using both descriptive non-compartmental analyses (NCA) and a population PK (Pop-PK) based compartmental analysis. In the formal PK studies, standard NCA approach was performed. Pharmacokinetic variables, e.g. AUC_{0-t}, AUC_{inf}, C_{max}, C_{min}, t_{max}, and $t_{1/2}$ were calculated according to standard procedures.

The Pop-PK analysis was conducted based on the non-linear mixed effects modelling approach. This approach estimated the typical (median) value of parameters and their variances. Model parameter estimation and model evaluation were implemented with NONMEM 7.2.

Absorption

Darolutamide consists of two diastereomers [(S,R) darolutamide and (S,S) darolutamide] which interconvert via the main circulating metabolite called keto darolutamide. Two studies, study 17831 (mass-balance + iv administration) and study 17830 (bioequivalence) informed darolutamide absorption.

Darolutamide is absorbed within the 6h hours after drug administration.

After oral administration of 300 mg [^{14}C]darolutamide given as a solution under fasted conditions in comparison to an intravenous dose, approximately 100% of the compound is absorbed and becomes bioavailable. When the same dose is given as a tablet under fasted conditions, approximately 30% of darolutamide becomes bioavailable indicating limited solubility and incomplete absorption. Absorption of darolutamide from a tablet formulation was increased by a factor of 2.0-2.5-fold (corresponding to 60-75% of darolutamide absorbed) when given together with a high-fat or a low-fat meal (fasted T_{max} = 3h vs fed T_{max} = 6h). A similar increase of exposure was observed for the major metabolite keto darolutamide.

The PK of darolutamide, each of the two diastereomers, and the active metabolite ketodarolutamide was determined in the PK subset (388 patients) of Study 17712. Individual area-under-the-curve from time zero to 12 hours at steady state (AUC(0-12)ss) and individual maximal and minimal concentrations at steady state (Cmaxss, Cminss) were calculated for the PK population using the selected Phase 3 popPK model after 15 days of nominal Q12h dosing of 600 mg b.i.d. using numerical integration. Following repeated oral administration of 600 mg b.i.d, peak plasma concentrations of darolutamide of 4.79 mg/L (coefficient of variation: 30.9%) are usually reached around 4 hours after administration. A geometric mean AUC(0-12) at steady-state of 52.8 h·µg/mL was calculated for nmCRPC patients which is 1.8-fold higher compared to the AUC(0-12) in healthy volunteers. Accordingly, the effective half-life representing the accumulation of darolutamide increases from 13 hours in healthy volunteers to approximately 20 hours in nmCRPC patients. The respective half-life values for (S,R)-darolutamide and (S,S)-darolutamide were 9 and 22 hours, respectively (see also sub-section on elimination). In parallel, the ratio of the two diastereomers changed from a 1:1 ratio in the tablet to an

approximately 1:9 ratio in plasma in these patients at steady-state. Due to the different effective half-lives in nmCRPC patients, steady-state of (S,R)-darolutamide is reached after 2 days and that of and (S,S)-darolutamide after 5 days following repeated b.i.d. dosing together with food.

Bioequivalence

Three drug product forms were used throughout the drug development: tablet A, tablet B and capsules. These three drug forms were compared in a formal clinical trial, study 17830, which was open-label, randomized, uncontrolled, multicenter Phase 1 clinical study of darolutamide in patients (N=30) with chemotherapy-naïve mCRPC. The study consisted of two components: a 3-period crossover PK component. Two concurrent groups, evaluating 2 separate test products, Tablet A and Tablet B. There was a 600 mg single dose administration of darolutamide 600 mg in the PK Component: 1) tablets administered in the fed state, 2) tablets administered in the fasted state and 3) capsules administered in the fed state. Subjects were randomised to one of the 2 test tablets and to one of 3 treatment sequences. There was a wash-out period of at least 7 days between study treatment administrations.

These formulations were bioequivalent based on the dedicated study (study 17830).

Distribution

Based on study 17831 in healthy volunteers following intravenous administration of 100 µg of [14C]darolutamide, the apparent volume of distribution was 119 L indicating that darolutamide is widely distributed throughout the body to both intracellular and extracellular fluid spaces.

In vitro plasma protein binding of the two diastereomers (S,R) and (S,S) darolutamide is moderate in human plasma with a mean free fraction of 8%, whereas the metabolite ketodarolutamide mean free faction is lower and estimated to 0.2%.

Elimination

Elimination parameters were based on the mass-balance study 17831 in healthy volunteers with (N=6), study 17830 based on the bioavailability study comparing two drug forms and food effect in mCRPC patients (N=2x15) and population PK analysis including the pivotal study (study 17712) in nmCRPC patients (N=388, PK subset).

Darolutamide is mainly excreted via urinary route by 63.4% based on the mass-balance study (study 17831) with 7% excreted unchanged, and via faeces by 32.4% with 30.7% unchanged fraction. More than 95% of the dose was recovered within 7 days after administration.

The renal clearance were estimated to 134.85 mL/min for (S,R)-darolutamide and 91.84 mL/min for (S,S) darolutamide. The ratio [(S,S):(S,R)] was estimated to be 1.46. These renal clearances normalized by eGFR are estimated 1.58 for (S,R)-darolutamide and 1.07 for (S,S)-darolutamide.

The effective half-life of darolutamide and keto darolutamide in plasma of patients is approximately 20 hours. Of the two diastereomers comprising darolutamide, (S,R) darolutamide has a shorter effective half life of 9 hours compared to (S,S) darolutamide with an effective half life of 22 hours. The clearance of darolutamide following intravenous administration was 116 mL/min (CV: 39.7%).

(S,R)-darolutamide half-life was two-fold shorter than the (S,S)-diastereomer due to the preferential back conversion of the metabolite (ketodarolutamide) into the (S,S) diastereomer.

Metabolism

The human metabolism was identified with the metabolism profiling of samples collected from the mass-balance study (study 17831). The enzymes involved in darolutamide main metabolites formation are CYP3A4 for ketodarolutamide and UGT1A9, UGT1A1, and UGT1A3 for O-glucuronides formation.

Following single oral administration of 300 mg ^{14}C-darolutamide given as an oral solution, keto-darolutamide is the only major metabolite with about 2-fold higher total exposure in plasma compared to darolutamide. Darolutamide and keto-darolutamide accounted together for 87.4% of the ^{14}C-radioactivity in plasma indicating that all other metabolites are of minor importance.

Darolutamide is metabolised primarily by oxidative metabolism mediated mainly by CYP3A4, as well as by direct glucuronidation mediated preferentially by UGT1A9 and UGT1A1. In addition, mainly the AKR1C isoforms were shown to catalyse the reduction of keto-darolutamide to the substance diastereomers.

The main active metabolite ketodarolutamide is formed by mainly CYP3A4 and to a lesser extent CYP1A1. This metabolite was found at 58.8% of the total dose (based on the total radioactivity from the mass-balance study) in plasma with only minor excretion as unchanged keto-darolutamide metabolite (0.6%) in faeces.

The other metabolites were drug O-glucuronides M-7 (25.5% of dose), drug N-glucuronides M-15 (5.75% of dose), and pyrazole sulfate metabolite M-29 (6.2% of dose). The unlabelled pyrazole metabolites M-32, M-33, M-34 and M-36 represented only minor metabolites.

Clinical studies (studies 17830, 17831, 17829) showed an increase in the diastereomers ratio based on the exposure ratio [(S,S):(S,R)] of approximately [5:1] to [6:1] and a linear increase in plasma concentration ratio between the two diastereomers with time. This supported the back-conversion of the metabolite, ketodarolutamide into (S,S)-darolutamide.

Based on population PK parameters estimated using the pivotal study (study 17712) in nmCRPC patients receiving 600 mg bid orally, ketodarolutamide Tmax was 2h which is similar to (S,R)-darolutamide and two hours earlier than (S-S) darolutamide Tmax. Ketodarolutamide half-life was close to the main diastereomer (S,S) and the metabolite's exposure was also almost 1.6 fold greater than the parent compound, i.e. darolutamide (as the sum of the two parent diastereomers).

Dose proportionality and time dependencies

A formal dose escalation was performed in mCRPC patients with increasing dose from 100 mg b.i.d. up to 900 mg with food. The dose dependency was tested by a linear regression all doses included.

In the dose range of 100 to 700 mg (after single dose and at steady state), the exposure to the two diastereomers and the major metabolite keto darolutamide increases linearly in a nearly dose related manner. Based on a saturated absorption, no further increase in exposure to darolutamide was observed at 900 mg twice daily.

Darolutamide steady state was assessed in the dose escalation study (study 17829). It was achieved within 7 days which is consistent with the effective half-life at steady state of approximately 20h. The accumulation ratios were estimated to 1.96 [1.71-2.26] (95% confidence interval) and 2.4 [2.13-2.77]) for $AUC_{(0-t)}$ and C_{max} respectively.

Population PK modelling

An exploratory population PK (pop-PK) analysis was performed for (S,R)-, (S,S)- darolutamide and ketodarolutamide following multiple oral dose of darolutamide (report 18651).

The analysed datasets included a total of 555 patients and 3158 samples from two datasets: the pivotal phase 3 study 17712 (in nmCRPC patients with sparse sampling on day 15, day 29, and week 23) and the pool of two phase 1/2 studies 17829 and 17830 (in mCRPC patients with rich PK sampling to describe the absorption phase). These data from phase 1/2 were box-cox transformed (right skewed distribution) and fitted simultaneously with the untransformed phase 3 data (normally distributed).

The final PK model consisted in two central compartments, one for each diastereomer. (S, R)-darolutamide absorption phase was described by 4 transit compartments, whereas (S,S)-darolutamide absorption was modelled with one depot compartment. From the two central compartments of each diastereomer, the two parent compounds are metabolized into a single compartment representing the active metabolite ketodarolutamide.

Error terms were estimated for each study with two types of error model applied: additive error model for the Box-Cox transformed dataset (i.e. phase 1/2, namely study 17829 and study 17830) and proportional error for the phase 3 study dataset (study 17712). In general, for the two diastereomers and the active metabolite, ketodarolutamide, the variabilities on the residual error terms were heterogeneous in the three datasets used (studies 17829 and 17830 box-cox transformed and study 17712 not transformed).

For (S,R)-darolutamide, the variability on the additional error terms on Box Cox transformed data were reasonable (CV% = 20.8% for study 17829 and CV%=28.4% for study 17830), whereas it was moderate for the proportional error term in study 17712 (CV%=37.10%).

For (S,S)-darolutamide, the variabilities on error terms were only acceptable for study 17829 (BC transformed CV=21.2%) and study 17712 (CV=24.4%) and moderate for study 17830 (BC-transformed CV=32.4%)

For the ketodarolutamide, the variabilities on error term were only acceptable for study 17830 (BC transformed CV=23.3%), whereas it was moderate for study 17829 (BC-transformed CV=38.7%) and study 17713 (CV=33.6%).

The estimated clearance was 4.58 L/h which appears to be consistent the estimated data using NCA analysis on formal clinical study (CL= 6.78 L/h, i.e. 116 mL/min from report R-11003 of study 17831). The estimated $T_{max,ss}$ by the pop-PK model were within the range of the observed data in mCRPC patients from the dose escalation study 17829 (1.84 h estimated vs 2h for (S,R)-darolutamide; and 4.73 h estimated vs 4h for (S,S)-darolutamide).

Darolutamide was found to be extensively distributed as evidenced by large apparent volume of distribution. The estimated distribution volume of 159-198L (Vd= 119 L and F= 60-75% from report R-11003 of study 17831) and estimated clearance (4.58 L/h IC95% [4.41 - 4.75]) were not consistent with the observed data (V/F= 44.5 L and CL= 7L/h).

Inter-individual variability (IIV) was modelled using a full variance-covariance matrix. IIV for CL was moderate for CL/F (CV% =39.5%) and high for KA 1,2,3 (54.6%).

Overall, the population typical values were precisely estimated (low RSE<15% for the fixed effects with exception of TFAST (RSE%=17.99%), ACAP (RSE%=17.94%), AFAST (RSE%=17.25%)).

Special populations

Gender

The PK of darolutamide, its major metabolite keto-darolutamide and diastereomers revealed a small effect with up to 1.7-fold higher exposure (AUC) and 1.3- to 1.5-fold higher maximum plasma concentrations, as well as prolonged terminal half-lives in females compared to males in study 17723 (darolutamide t1/2= 11.6 h in male and 15.8 h in female).

Race

Exposure of darolutamide observed in 9 Japanese patients with prostate cancer (mCRPC) in study 17719 was in the same range compared to Caucasian patients with mCRPC evaluated in previous studies, but the exposure was at the upper end of that range.

Similar data were observed in the Phase 3 study 17712. A population PK analysis showed an approximately 1.4-fold higher mean $AUC(0\text{-}12)_{ss}$ in patients in the Japanese region compared to patients from all other regions. However, there was still a large overlap of the exposure in Japanese compared to the exposure in patients from the other regions.

Weight

No effect of body weight was concluded based on the population PK covariate analysis.

Age

No effect in the elderly (by age group <65 years, 65 ≤years<75, 75 ≤years<85, ≥85 years) was concluded based on the population PK covariate analysis.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	93	50	2
Population PK	140	163	44

Hepatic impairment

In a clinical pharmacokinetic study following a single dose 600 mg darolutamide administration C_{max} and AUC for darolutamide were 1.5 and 1.9-fold higher in patients with moderate hepatic impairment (Child-Pugh B) compared to healthy volunteers. There are no data for patients with severe hepatic impairment (Child-Pugh C).

Renal impairment

In a clinical pharmacokinetic study following a single dose 600 mg darolutamide administration, AUC and C_{max} for darolutamide were 2.5 and 1.6-fold higher in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] 15 to 29 mL/min/1.73 m^2) compared to healthy volunteers.

A population pharmacokinetic analysis indicates a 1.1-, 1.3- and an approximately 1.5-fold higher exposure (AUC) of darolutamide in patients with mild, moderate and severe renal impairment (eGFR 15 to 89 mL/min/1.73 m^2) compared to patients with normal renal function.

Pharmacokinetic interaction studies

Based on in vitro data, three clinical interaction studies were conducted to assess the magnitude of the potential interactions with darolutamide.

Effect of darolutamide on rosuvastatin pharmacokinetics (Study 17723)

Primary Objective	The primary objective was to evaluate the potential perpetrator effect of darolutamide on rosuvastatin pharmacokinetics (PK)
Design	Single-center, non-randomized, fixed-sequence, two-period design
Population N:Entered/ Analyzed	Healthy White male or female subjects (in postmenopausal state) between 45 and 65 years of age with a body mass index between 18.0 (inclusive) and 29.9 kg/m2 (inclusive) N: 30 (15 males 15 female) / 29 (15 males/ 14 females)
Treatments	Period 1: rosuvastatin 5 mg single dose on Day 01 Period 2: rosuvastatin 5 mg single dose administrations on Day 08 single darolutamide 600 mg on Day 01, and multiple dose administrations of 600 mg twice daily for 5 days (Day 04 to Day 08)

Results from the present study demonstrated a substantial effect of darolutamide on the PK of the transporter substrate rosuvastatin. AUC(0-24) and Cmax of rosuvastatin given in combination with darolutamide under steady state conditions and in the fed state were approximately 5-fold higher compared to those parameters of rosuvastatin given alone. However, time to reach peak plasma concentrations and the elimination rate of rosuvastatin was not influenced by comedication of darolutamide. Likewise, the renal clearance of rosuvastatin did not change during co-medication with darolutamide.

Effect of darolutamide on midazolam pharmacokinetics (Study 18860)

Primary Objective	To evaluate the effect of darolutamide on the pharmacokinetics (PK) of CYP3A Substrate (midazolam) To evaluate the effect of darolutamide on the PK of P-gp substrate (nonconjugated dabigatran)
Design	Single center, open-label, non-randomized, fixed-sequence, three periods
Population N:Entered/ Analyzed	Healthy male, 45 to 65 years of age (inclusive) N: 15/13
Treatments	Period 1: dabigatran 75 mg single dose + midazolam 1 mg D01 Period 2: darolutamide 600 mg b.i.d. D1 to D11 + 75 mg dabigatran D09 + 1 mg midazolam D09

Concomitant dosing of MDZ with 600 mg BID darolutamide on Day 9 of BID darolutamide treatment led to a decrease of approx. 29% and 22% in AUC of MDZ and 1-OH midazolam, respectively. Likewise, maximum plasma concentrations decreased by approx. 32% for both MDZ and 1-OH midazolam when compared to dosing of MDZ without darolutamide.

Darolutamide decreased total AUC of non-conjugated and total dabigatran by 9% and 12% respectively. This decrease was slightly more pronounced for Cmax (16% and 17% decrease for non-conjugated and total dabigatran, respectively).

Effect of other drugs on darolutamide pharmacokinetics (Study 17726)

Primary Objective	Evaluate the effect of itraconazole, a strong CYP3A4 inhibitor, on the pharmacokinetics (PK) of darolutamide, its diastereomers (S,R)- darolutamide and (S,S)- darolutamide and major

	metabolite keto-darolutamide.
Design	Single center, open-label, non-randomized, fixed-sequence, three periods
Population N:Entered/ Analyzed	Healthy male, 45 to 65 years of age (inclusive) N: 15/15
Treatments	Period 1: darolutamide 600 mg single dose D01 Period 2: darolutamide 600 mg single dose D05 + 100 mg itraconazole b.i.d. D01 then D02 to D07 (multiple dose) Period 3: darolutamide 600 mg single dose D08 + 600 mg rifampicin D01 to D10

Concomitant administration of darolutamide with the CYP3A4 and P-gp inhibitor itraconazole or the CYP3A4 inducer rifampicin at steady state had a marked effect on the PK of darolutamide, its diastereomers and major metabolite. Concomitant administration of itraconazole resulted in 1.75-, 1.70-, 1.76- and 1.80-fold higher mean AUC(0-72) and in 1.36-, 1.50-, 1.38- and 1.39-fold higher mean maximum plasma concentrations of darolutamide, (S,R)-, (S,S)- and keto-darolutamide, respectively, thus classifying darolutamide as weakly sensitive to inhibition of CYP3A4. Concomitant administration of rifampicin led to a decrease to 28, 24, 29 and 25% of mean AUC(0-72) and a decrease to 48, 37, 51 and 47% of mean maximum plasma concentrations of darolutamide, (S,R)-, (S,S)- and keto-darolutamide, respectively, compared to darolutamide alone.

2.4.3. Pharmacodynamics

Mechanism of action

Darolutamide is an androgen receptor (AR) inhibitor with a flexible polar substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain. Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. A major metabolite, keto-darolutamide, exhibited similar *in vitro* activity to darolutamide. Darolutamide treatment decreases prostate tumour cell proliferation leading to potent antitumour activity (see SmPC section 5.1).

Primary and Secondary pharmacology

Primary pharmacodynamics

Prostate-specific antigen (PSA) is a protein produced by prostate cells and is an established biomarker of disease management in prostate cancer. Expression of the PSA gene is directly regulated by binding of AR and therefore darolutamide is expected to negatively regulate the PSA levels. A PSA response was observed in the pivotal Phase 3 study in nmCRPC, with 83.6% of the patients having ≥50% decline in the serum PSA levels in the darolutamide arm. Comparable decreases in serum PSA levels were also seen in the supportive Phase 1/2 studies with the metastatic patient population. The best responses were seen in the chemo-/CYP17i naïve subgroup (85.7% of the patients showed a PSA decline ≥50% in one study and 83.3% of the patients in another study).

In addition, an exploratory exposure-PSA analysis was conducted to investigate the relationship between the exposure of darolutamide and change in PSA over time (see section below on exposure efficacy relationship).

Darolutamide treatment had a positive effect on circulating tumour cells (CTC) counts, which decreased at all studied dose levels in the Phase 1/2 Study 17829.

Pharmacodynamic serum hormone variables such as testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and DHT did not show any clinically relevant changes in mCRPC patients on ADT during treatment with darolutamide and were therefore not evaluated in subsequent clinical studies, including studies in nmCRPC patients.

Additional biomarkers evaluated in mCRPC include bone alkaline phosphatase (bALP), procollagen type I amino-terminal propeptide (P1NP), chromogranin A (CgA), and serine protease inhibitor Kazal type 1 (SPINK1), AR and ERG (TMPRSS2-ERG fusion expression). No clear association was observed with AR molecular status (copy number and mutations) and PSA response at Week 12. No clear association of ERG or SPINK1 expression status in archival tumour tissue samples and PSA response at Week 4 or Week 12 was observed.

Exposure-response relationship

Study 19792

Title: Exploratory population pharmacodynamic analysis of change in prostate specific antigen over time in studies 17712, 17829 and 17830.

The relationship between exposure and PSA was investigated using a covariate Pop-PD model with exposure as covariate. The model was adapted from Desmée et al. (2015) published model for prostate-specific antigen kinetics and link with survival in the context of metastatic prostate cancer. Two additional parameters were added: EM is the maximal log(PSA) reduction achieved with active treatment and ER is the decay rate constant of the treatment effect.

The used exposures were simulated from the presented POP-PK model. They were related to EM parameter, the maximal PSA reduction achieved, by an Emax model. Other than exposure, other covariates were identified based on the forward/backward covariate selection.

The proliferation rate was faster for patients with lower PSA Doubling Time. Higher haemoglobin at baseline and chemotherapy and CYP17 inhibitor naïve patients were found to show a greater maximum decrease in PSA.

A dose of 600 mg bid resulted in close to maximum PSA reduction from baseline for chemotherapy and CYP17 inhibitor naïve patients in both the phase 1-2 and phase 3 population.

Study 18962

Title: Exploratory exposure-response analysis of metastatic free survival (MFS) and darolutamide exposure, and of MFS and change in prostate specific antigen (PSA) under treatment with darolutamide in study 17712.

Data from 1419 patients of study 17712 without baseline metastasis were used in this E-R analysis.

PSA doubling time (PSADT) and PSA concentration (below or above population median) at baseline were significantly associated with MFS. Patients with a low PSADT (<25th percentile) and high PSA concentration (>median) at baseline experienced shorter MFS compared to patients with high PSADT (>75th percentile) and low PSA concentration (≤ median) at baseline.

The maximum decrease in PSA from baseline was significantly associated with MFS for all patients treated with darolutamide. The fraction of patients surviving without metastases after 1 year of darolutamide

treatment is predicted to range from approximately 95% for patients with a close to 100% decrease in PSA from baseline to approximately 80% for patients with a considerably lower decrease in PSA from baseline of around 40%.

MFS was found to be consistent over the observed exposure range in Study 17712. The fraction of patients surviving without metastases after 1 year of darolutamide was predicted to be greater than 90% for 90% of the subjects irrespective if the analysis was based on the PK subset or on all darolutamide treated patients.

Secondary pharmacodynamics and cardiac safety

Study 19557

This was an exploratory study which used concentration-QTc (C-QTc) modelling to assess the QTc interval prolongation risk of darolutamide based on data in a subset of patients from the phase 3 study 17712 in which triplicate ECG recordings with matched PK sampling were collected. All patients included in study 17712 received the proposed therapeutic dose of 600 mg bid.

The results of this ECG study showed no clear signal of any effect of darolutamide on heart rate, AV conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were relatively balanced rates of new clinically relevant morphological changes in the darolutamide and placebo arms, except for a higher incidence of atrial fibrillation and atrial flutter in the darolutamide treatment arm (though 50% of these patients had a prior history of atrial tachyarrhythmias).

There also was no signal of any effect of darolutamide on cardiac repolarization as evidenced by the results of the by time point analysis in a separate evaluation of the effect of darolutamide concentration on the QTc interval in a PK subset of patients with nmCRPC.

QTcF (QT interval corrected for heart rate using the Fridericia's formula) was used in the concentration-QTc analysis. The results of the time-averaged and outlier analyses showed that darolutamide has no effect on cardiac repolarization. In addition, an evaluation of any possible darolutamide concentration-QT interval (QTcF) relationship showed that the upper limit of the 90% confidence interval (CI) of the estimated difference in QTcF from baseline and placebo (ΔΔQTcF) at any concentration did not exceed the threshold of 10ms due to a negative slope of the concentration-QTcF relationship.

The ECG results from the dedicated PK subset analysis in nmCRPC patients were consistent with those of the total safety population of the Phase 3 study in nmCRPC.

2.4.4. Discussion on clinical pharmacology

Three drug products forms were used throughout the drug development: tablet A, tablet B and capsules. These formulations were bioequivalent based on the dedicated study (study 17830) (data not shown).

The pharmacokinetics profile has been sufficiently characterised. The estimated volume of distribution of darolutamide was larger than the whole body fluid volume suggesting tissue distribution.

Darolutamide is moderately (92%) bound to human plasma proteins without any difference between the two diastereomers. The major metabolite of darolutamide, keto-darolutamide, is highly (99.8%) bound to plasma proteins. Given the very low free-fraction of the metabolite, keto-darolutamide contribution to the activity is unlikely.

Passage of darolutamide across the blood brain barrier has not been studied clinically. However, brain exposures to darolutamide in terms of AUC(0-24) are very low with 4.5% of plasma exposure after single dose in rats and 1.9-3.9% after repeated dose in mice (see non-clinical aspects). This indicates low passage of darolutamide across the intact blood brain barrier in rats and mice and a low likelihood that darolutamide crosses the intact blood brain barrier in humans to a clinically relevant extent (see SmPC section 5.2).

The diastereomers (S,R) darolutamide and (S,S) darolutamide are able to interconvert via the metabolite keto-darolutamide. Presented data are consistent with a back conversion of the metabolite ketodarolutamide into preferentially (S,S)-darolutamide. A back-conversion-mediated by AKR1C3 and to a lesser extent AKR1D1 was also reported. The human aldo-keto reductases (AKRs) is a super family of NAD(P)H linked oxido-reductases. The enzymes family were reported to be highly polymorphic with some SNPs of high penetrance (Penning and Crury, 2007). The impact of the AKR1C polymorphism review (Alshogran, 2017) highlighted limited available information on PK which leads to uncertainty on the clinical relevance of this enzyme polymorphism.

Glucuronidation is expected to contribute by 32.6% to the total drug clearance which is not negligible. The potential impact clinical impact of UGT polymorphism was discussed based on literature review and its clinical consequences on exposure are considered limited.

The drug is mainly excreted by renal passive glomerular filtration and tubular secretion. The two diastereomers clearance was overall comparable.

The dose linearity over the range 100 up to 700 mg is agreed. The proposed indicated dose of 600 b.i.d is covered by the dose linearity.

With regards to special population, a formal study was conducted to assess gender effect in healthy volunteers. Darolutamide showed a gender effect with 1.3- to 1.7-fold higher exposure and maximum plasma concentrations as well as prolonged terminal half-lives in females. However, given the target population is patients with non-metastatic castration-resistant prostate cancer, it is agreed that the gender effect is not relevant for this indication.

No clinically relevant differences in the pharmacokinetics of darolutamide were observed based on ethnicity (White, Japanese, non-Japanese Asian, Black or African American). A population pharmacokinetic analysis indicated a 1.4 fold increase in exposure (AUC) in Japanese patients compared to patients from all other regions. (see SmPC section 5.2).

Furthermore, no clinically relevant differences in the pharmacokinetics of darolutamide were observed based on age (48-95 years). No dose adjustment is necessary in elderly patients (see SmPC sections 4.2 and 5.2).

Regarding paediatric population, there is no relevant use of darolutamide in the paediatric population for the indication of treatment of nmCRPC (see SmPC section 4.2).

The available data in patients with moderate hepatic impairment are limited, and darolutamide has not been studied in patients with severe hepatic impairment. Following a single dose 600 mg darolutamide administration, a 1.9-fold increase in darolutamide exposure (AUC0-48h) was observed in patients with moderate hepatic impairment. Thus, for patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily (see SmPC sections 4.2, 4.4 and 5.2.). As exposure might be increased those patients should be closely monitored for adverse reactions (see sections 4.2, 4.4 and 5.2). No dose adjustment is necessary for patients with mild hepatic impairment.

Following a single dose 600 mg darolutamide administration, there was a 2.5-fold increase in darolutamide exposure in patients with severe renal impairment. For patients with severe renal impairment (eGFR

15-29 mL/min/1.73 m^2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily (see SmPC sections 4.2, 4.4 and 5.2). As exposure might be increased those patients should be closely monitored for adverse reactions (see SmPC sections 4.2 and 5.2). No dose adjustment is necessary for patients with mild or moderate renal impairment.

The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR < 15 mL/min/1.73 m^2) (see SmPC section 5.2).

In vitro studies showed that darolutamide is a UGT1A9, UGT1A1, UGT1A3 substrate and UGT1A9, UGT1A1 inhibitor (see non-clinical section). The Applicant considered clinical DDI studies with UGT isoform-selective inhibitors not necessary given the threshold of 25% for enzymes contributing to a drug elimination pathway. It is agreed there is no need to perform a clinical study to evaluate inhibition for UGT1A1, as atazanavir metabolism may be induced by darolutamide.

With regards to darolutamide potential to inhibit UGT1A9, an AUCR of 1.11 was calculated for the extent of an interaction of the diastereomer (S,R)-darolutamide with a sensitive UGT1A9 substrate, e.g. dapagliflozin. As this value is lower than the threshold AUCR value of 1.25, these data do not indicate a risk for perpetrator drug-drug interaction resulting from UGT1A9 inhibition by darolutamide. In relation to darolutamide being a UGT1A9 substrate the applicant presented literature data and real data from nmCRPC patients who took UGT inhibitors concomitantly showing an expected darolutamide exposure increase in the range of 1.2- and 1.5-fold when darolutamide is given together with an UGT inhibitor compared to given alone. A population pharmacokinetic analysis showed that co-administration of UGT1A9 inhibitors with darolutamide resulted in a 1.2-fold increase in exposure (AUC_{0-72}) of darolutamide. No clinically relevant drug-drug interaction is expected in case of UGT1A9 inhibitor administration. Darolutamide may be given concomitantly with UGT1A9 inhibitors (see SmPC section 4.5).

Darolutamide is also a substrate of CYP3A4, P-gp and breast cancer resistance protein (BCRP). Administration of itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days), a strong CYP3A4, P-gp and BCRP inhibitor, with a single dose of darolutamide (600 mg on day 5 together with food) resulted in a 1.7-fold increase in mean exposure (AUC_{0-72}) and a 1.4-fold increase of C_{max} of darolutamide. No clinically relevant drug-drug interaction is expected in case of CYP3A4, P-gp or BCRP inhibitor administration. Darolutamide may be given concomitantly with CYP3A4, P-gp or BCRP inhibitors. Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure which may increase the risk of darolutamide adverse reactions. It is recommended to monitor patients more frequently for darolutamide adverse reactions and modify darolutamide dose as needed (see SmPC section 4.5).

Repeated administration of rifampicin (600 mg), a strong CYP3A4 and a P-gp inducer, with a single dose of darolutamide (600 mg) together with food, resulted in a decrease of 72% in mean exposure (AUC_{0-72}) and a decrease of 52% in C_{max} of darolutamide. The use of strong and moderate CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort, phenytoin, and rifampicin) during treatment with darolutamide may decrease the plasma concentration of darolutamide and is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered (see SmPC sections 4.4 and 4.5).

The clinical DDI studies (Study 17723 with rosuvastatin, BCRP/OATP1B1/OATP1B3 inhibitor) showed darolutamide is an inhibitor of breast cancer resistance protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3. Administration of darolutamide (600 mg twice daily for 5 days) prior to co-administration of a single dose of rosuvastatin (5 mg) together with food resulted in approximately 5-fold increase in mean exposure (AUC) and C_{max} of rosuvastatin. Co administration of darolutamide with other

BCRP substrates should be avoided where possible. Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin).

Therefore, it is recommended to monitor patients for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates, as co-administration with darolutamide may increase the plasma concentrations of these substrates. Co administration with rosuvastatin should be avoided unless there is no therapeutic alternative Selection of an alternative concomitant medicinal product with less potential to inhibit BCRP, OATP1B1 and OATP1B3 should be considered (see SmPC sections 4.4 and 4.5).

Co-administration of darolutamide together with the sensitive P-gp substrate dabigatran etexilate did not reveal any increase in exposure (AUC and C_{max}) of dabigatran. No clinically relevant drug-drug interaction is expected in case of P-gp substrate administration. Darolutamide may be given concomitantly with P-gp substrates (e.g. digoxin, verapamil or nifedipine).

Darolutamide is a mild inducer of CYP3A4. No clinically relevant drug-drug interaction is expected in case of CYP substrate administration. Darolutamide may be given concomitantly with CYP substrates (e.g. warfarin, L-thyroxine, omeprazole). Administration of darolutamide (600 mg twice daily for 9 days) prior to co-administration of a single dose of the sensitive CYP3A4 substrate midazolam (1 mg) together with food, decreased the mean exposure (AUC) and C_{max} of midazolam by 29% and 32%, respectively.

Darolutamide is a weak CYP3A4 inhibitor *in vitro* but not with clinical significance. Darolutamide did not inhibit the metabolism of selected CYP substrates *in vitro* at clinically relevant concentrations.

In terms of pharmacodynamic data, PSA was used as surrogate biomarker which is considered appropriate. In general, the observed change from baseline in serum PSA showed that darolutamide has a clinically meaningful antitumour activity in mCRPC and nmCRPC patients. The conducted studies showed darolutamide decreased the level of PSA by over 50% in 83.3% to 85.7% of the patients in pivotal (83.6% of the patients) and supportive studies.

From the population PK (POP-PK) model, the PSA doubling time, the haemoglobin rate at baseline and the chemotherapy and CYP17 inhibitor treatment status were identified as significant covariates on darolutamide efficacy. The lower the PSA doubling time, the faster the cancer cells proliferation rate was. The higher the haemoglobin rate, the greater the decrease in PSA was. If patients were treatment naïve, the decrease in PSA was higher.

With regards to exposure-response relationship, the observed change in PSA over time in both the phase 1-2 and phase 3 populations was adequately described by a previously published population PD model, which linked tumour proliferation to PSA turnover in the blood. The association between darolutamide exposure and the maximum change in PSA from baseline was best described with an Emax type model, which indicates that the PSA lowering effect of darolutamide reaches a maximum at higher exposure. The results suggested that a dose of 600 mg bid results in close to maximum PSA reduction from baseline for chemotherapy and CYP17 inhibitor naïve patients in both the phase 1-2 and phase 3 population.

Study 18962 indicated that the relationship between darolutamide exposure and MFS is flat, which is in line with the analyses of the association between exposure and change in PSA, and between change in PSA and MFS. This suggests that, at the proposed dose of darolutamide 600 mg bid, the maximum response with respect to both PSA decrease and MFS is achieved.

With respect to pharmacodynamics related to safety, the cardiac activity was monitored in patients receiving darolutamide treatment. No prolongation of the mean QTcF interval (i.e., greater than 10 ms) was observed

after oral administration of 600 mg darolutamide twice daily compared to placebo (see SmPC section 5.1). The results of an ECG study in a PK subset of patients with nmCRPC showed no clear signal of any effect of darolutamide on heart rate, AV conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were relatively balanced rates of new clinically relevant morphological changes in the darolutamide and placebo arms, except for a higher incidence of atrial fibrillation and atrial flutter in the darolutamide treatment arm (though 50% of these patients had a prior history of atrial tachyarrhythmias) (see also discussion on clinical safety).

Overall, the pharmacodynamics of darolutamide have been sufficiently characterised. Although the clinical PD studies were exploratory in nature, the findings appear to support the proposed darolutamide dose of 600 mg bid.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of darolutamide has been sufficiently characterised.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Darolutamide was studied in the dose range from 100 to 900 mg b.i.d. in the dose escalation and dose finding study 17829 (ARADES). Dose-linearity of the pharmacokinetic parameters was observed after single and repeated administration in the dose range of 100 to 700 mg darolutamide b.i.d. At a higher dose (900 mg b.i.d.), no further increase in the exposure and maximum concentration of darolutamide was observed, indicating that saturation of absorption may occur at doses higher than 700 mg of darolutamide b.i.d..

The results of the expansion part of study 17829 (ARADES) suggest that the 700 mg b.i.d. dose is as safe and tolerable as the 100 or 200 mg b.i.d. dose levels. Independent of the dose (100, 200 or 700 mg b.i.d.), the best PSA responses were seen in the chemo-/CYP17i-naïve subgroup compared to the post-chemo/CYP17i-naïve subgroup and the post-CYP17i subgroup. A dose-related response was seen in the chemo-/CYP17i-naïve subgroup, with a higher percentage of patients in the 700 mg b.i.d. dose group achieving a decline in PSA (85.7%) compared to the lower dose groups of 100 mg (45.5%) and 200 mg b.i.d. (69.2%).

Study 17830 (ARAFOR) was conducted using a dose of 600 mg darolutamide b.i.d., a dose selected based on the initial results from study 17829 (ARADES) and non-clinical efficacy data in mice. Anti-tumour activity was demonstrated and darolutamide was well-tolerated in the study. Plasma exposure plateau was seen from 700 mg bd dose in the ARADES study and darolutamide plasma exposure after 600 mg bid in the ARAFOR study was similar to what was observed after 700 mg bid in the ARADES study.

2.5.2. Main study

Study ARAMIS 17712

Methods

This study was a randomized, double-blind, placebo-controlled, multi-center Phase 3 trial to evaluate darolutamide in patients with nmCRPC who are at high risk for developing metastases.

Study Participants

This multinational study was conducted in 36 countries/regions in North America (Canada and United States), Asia Pacific (Japan, South Korea, and Taiwan) and the rest of the world (Argentina, Austria, Australia, Belarus, Belgium, Brazil, Bulgaria, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Latvia, Lithuania, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Turkey, Ukraine, and the United Kingdom).

Inclusion criteria:

1. Written informed consent obtained.

2. Males aged ≥ 18 years.

3. Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features.

4. CRPC defined as 3 rising PSA levels after the nadir taken at least 1 week apart during ADT. If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after antiandrogen withdrawal. (modified by amendment 2)

5. Castrate level of serum testosterone (< 1.7 nmol/l [50 ng/dl]) on GnRH agonist or antagonist therapy or after bilateral orchiectomy. Patients who have not undergone bilateral orchiectomy must continue GnRH therapy during the study.

6. PSADT of ≤ 10 months and PSA ≥ 2 ng/ml at screening (modified by amendment 2).

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

8. Blood counts at screening: haemoglobin ≥ 9.0 g/dl, absolute neutrophil count ≥ 1500/µl ($1.5x10^9$/l), platelet count ≥ 100,000/µl ($100x10^9$/l) (patient must not have received any growth factor or blood transfusion within 7 days of the haematology laboratory obtained at screening).

9. Screening values of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 x upper limit of normal (ULN), total bilirubin ≤ 1.5 x ULN (except patients with a diagnosis of Gilbert's disease), creatinine ≤ 2.0 x ULN (modified by amendment 2).

10. Sexually active patients, unless surgically sterile, must agree to use condoms as an effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of the study treatment.

Exclusion criteria:

1. History of metastatic disease at any time or presence of detectable metastases by blinded central reading within 42 days prior to start of study treatment. Presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation is allowed.

2. Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer.

3. Acute toxicities of prior treatments and procedures not resolved to grade ≤ 1 or baseline before randomisation.

4. Prior treatment with: second generation AR inhibitors, CYP17 enzyme inhibitor such as abiraterone acetate, TAK-700 or oral ketoconazole longer than for 28 days.

5. Use of oestrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomization and AR inhibitors (bicalutamide, flutamide, nilutamide, cyproterone acetate) at least 28 days before screening (modified by amendment 2)

6. Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed > 2 years before randomization.

7. Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomization.

8. Radiation therapy (external beam radiation therapy, brachytherapy, or radiopharmaceuticals) within 12 weeks before randomization.

9. Severe or uncontrolled concurrent disease, infection or co-morbidity that, in the opinion of the investigator, would make the patient inappropriate for enrolment

10. Treatment with an osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomization. Patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule.

11. Known hypersensitivity to the study treatment or any of its ingredients.

12. Major surgery within 28 days before randomisation.

13. Any of the following within 6 months before randomization: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association Class III or IV.

14. Uncontrolled hypertension as indicated by a systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg at screening (*modified by amendment 2*).

15. Prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e. pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥ 5 years ago and from which the patient has been disease-free *(language harmonised by amendment 3)*.

16. Gastrointestinal disorder or procedure which expects to interfere significantly with absorption of study treatment.

17. Active viral hepatitis, active human immunodeficiency virus (HIV) or chronic liver disease.

18. Treatment with any investigational drug within 28 days before randomisation (*modified by amendment 2*).

19. Any condition that in the opinion of the investigator would impair the patients' ability to comply with the study procedures.

20. Unable to swallow study medications and comply with study requirements

Treatments

Darolutamide 300 mg film-coated tablets or placebo film-coated tablets for oral administration. Patients were instructed to take 2 tablets of study treatment orally bid at about 12-h intervals as close to the same time each day as possible. If dosing was delayed, dosing could be taken up to 6 hours to make up for the missed one. The tablets should be taken with food and a glass (about 250 ml) of water, milk or juice. The tablets should be swallowed whole.

Objectives

The primary objective of this study was to demonstrate superiority of darolutamide over placebo on MFS in patients with nmCRPC.

The secondary objectives of this study were to demonstrate the benefit of darolutamide compared with placebo for Overall Survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first Symptomatic skeletal event (SSE), and to characterise the safety and tolerability of darolutamide.

The additional objectives of this study were to determine the benefit of darolutamide on PFS, time to first prostate cancer-related invasive procedure, time to initiation of first subsequent antineoplastic therapy; and to determine the effect of darolutamide on PSA progression and PSA response, Eastern Cooperative Oncology Group (ECOG) performance status deterioration, health-related Quality of Life (QoL); and to evaluate the PK of darolutamide and keto-darolutamide, and to explore possible relationships between exposure and safety and efficacy response.

Outcomes/endpoints

The primary efficacy endpoint was MFS defined as time between randomisation and evidence of metastasis or death from any cause, whichever occurs first.

Chest, abdomen, and pelvic CT/MRI and nuclear medicine bone scan were to be performed at screening (baseline) and every 16 weeks until confirmed metastasis. Absence or presence of metastasis were to be confirmed by the independent blinded central reading during the double-blind treatment phase. Metastasis in bone was defined as appearance of 1 or more lesions that are confirmed by the central reading according to the one of the methods described below. If the central reading identifies changes on bone scan, confirmatory anatomic imaging CT/MRI or x-ray, of the area in question was to be obtained. Anatomic imaging performed up to 2 weeks prior to bone scan or later could be used as a confirmatory scan. Appearance of bone metastasis was to be assigned to the date of the bone scan at which the lesion was first identified.

Metastasis in non-osseous tissue was defined as new distant pathologic lymph nodes (M1a) or other pathological lesion (M1c) according to RECIST 1.1. New or progressive regional pathologic lymph nodes were not to be defined as metastasis.

The secondary efficacy endpoints of the study were:

- OS, defined as time from randomisation to date of death from any cause.

- Time to first SSE, defined as time from randomisation to the first occurrence of SSE (defined as occurrence of any of the following: external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumour related orthopaedic surgical intervention).

- Time to cytotoxic chemotherapy is defined as time from randomisation to initiation of the first cytotoxic chemotherapy.

- Time to pain progression: Pain progression was defined as an increase of ≥ 2 points from baseline (day 1 score) in question 3 of BPI-SF (related to the worst pain in the last 24 hours) taken as a 7-day average, or initiation of short or long-acting opioids for pain, whichever comes first. Pain was to be assessed with the BPI-SF questionnaire during the visit, pain diary entries from 6 days preceding the visit and opioid use from baseline until documented pain progression.

The additional efficacy variables of the study were:

- Progression Free Survival (PFS), defined as time between randomisation and evidence of any radiographic disease progression, including new pathologic lymph nodes identified above or below the aortic bifurcation or death from any cause, whichever occurs first.

- Time to first prostate cancer-related invasive procedure, defined as time from randomization to date of first prostate cancer-related invasive procedure. Prostate cancer-related invasive procedure was defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g. catheterisation of the bladder, percutaneous drainage of hydronephrosis, palliative electroresection of the prostate, etc.).

- Time to initiation of subsequent antineoplastic therapy, defined as time from randomization to initiation of first antineoplastic therapy.

- Time to PSA progression, was defined as the time from randomization to the date of first PSA progression. PSA progression was defined as an increase of PSA of ≥25% and an absolute increase of PSA of ≥2 ng/ml above the nadir, which was confirmed by a consecutive value obtained 3 or more weeks later. PSA progression was only declared if observed at week 16 or later after randomization.

The PSA progression definition deviated from PCWG2, as confirmation by a second value was requested for patients with no decline from baseline during treatment.

- Percent of patients with PSA response

The percentage change of PSA from baseline was to be calculated and the proportion of patients achieving a decline of ≥50% from baseline was to be determined.

- Percent of patients with ECOG performance status deterioration, defined as an increase to grade 3 or higher, with an increase of at least 2 from baseline.

- Time to ECOG performance status deterioration, as time from randomisation to ECOG performance status deterioration (an increase to grade 3 or higher, with an increase of at least 2 from baseline).

- Health-related QoL using FACT-P questionnaire, prostate cancer-specific subscale of the FACT-P questionnaire and generic EQ-5D-3L questionnaire.

Disease-specific FACT-P questionnaire: FACT-P was to be assessed at screening, day 1, week 16, and at the end-of-study treatment visit. For placebo patients crossing over to open-label darolutamide treatment, FACT-P was to be assessed at the start of open-label treatment instead of end-of-study treatment visit. Patients were to be defined as having total QoL deterioration, if they experienced a decrease of ≥ 10 points in FACT-P total score compared with baseline. The percent of patients experiencing deterioration in QoL from baseline based on the FACT-P total score at week 16 was to be determined.

Prostate cancer-specific subscale of the FACT-P questionnaire (PCS subscale of FACT-P): PCS subscale was to be assessed at screening, day 1 and every 16 weeks until the end of the follow-up period, and at the end-of-study treatment visit. For placebo patients crossing over to open-label darolutamide treatment, FACT-P was to be assessed at the start of open-label treatment instead of end-of-study treatment visit. Patients were to be defined as having QoL deterioration, if they experienced a change of ≥ 3 points in PCS compared with baseline (Cella D et al., 2009).

Generic EQ-5D-3L questionnaire: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression were each assessed on 3-point categorical scales ranging from "no problem" to "severe problem". EQ-5D-3L was to be assessed at screening, day 1, week 16, and at the end-of-study treatment visit to explore the impact of potential adverse effects on overall QoL. For placebo patients crossing over to open-label darolutamide, EQ-5D-3L was to be assessed at the start of open label treatment instead of end-of-study treatment visit. If the end of the double-blind treatment period occurred less than 16 weeks from the start of study treatment, the EQ -5D-3L assessment was required in the first 16 weeks of open-label darolutamide treatment. Patients were to be considered to have deterioration in overall QoL, if they experienced a deterioration of ≥ 0.06 points compared with baseline.

Sample size

The initial sample size calculation for the ARAMIS study was updated following publication of results from the SPARTAN (apalutamide) and PROSPER (enzalutamide) phase III clinical trials and conduct of a central efficacy review of baseline radiological scans which identified some patients with metastases at baseline. The assumptions used to determine the final sample size for the primary endpoint of MFS were as follows:

- Overall type I error rate: 0.05
- Statistical power at the final analysis: 91%
- Primary endpoint: MFS
- Median MFS for placebo: 25 months (based on denosumab phase III study results)
- Assumed hazard ratio of 0.65
- Diluted hazard ratio of 0.71 (accounting for presence of baseline metastases)
- Randomisation: 2:1

385 MFS events was found to provide approximately 91% power to detect a statistically significant difference in MFS times, using a log-rank test with a two-sided 0.05 level of significance. Assuming 40 months' accrual time and a dropout rate of 40%, the study was calculated to require approximately 1500 patients (1000

darolutamide patients, 500 placebo patients) to achieve approximately 385 MFS events within a reasonable time. The sample size calculation was performed with a simulation-based algorithm. No sample size calculations were performed for the overall survival endpoint.

Randomisation

All eligible patients were randomised to receive darolutamide 600 mg twice daily or placebo in a 2:1 ratio in a double-blind manner. Randomisation was stratified by PSA doubling time (PSADT; ≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).

Blinding (masking)

The pivotal study was a double blinded trial with a subsequent open label part. The double-blind part was planned to be continued until the total number of MFS events for primary analysis were reached (at about 385 events). Patients in the placebo arm at the time of the planned study treatment code unblinding, were to be offered the opportunity to receive darolutamide through open-label treatment if there was a positive benefit/risk assessment at the primary analysis in favour of darolutamide

Statistical methods

Analysis sets

The Full Analysis Set (FAS) included all randomized patients.

The Safety Analysis Set (SAF) was the primary population for safety analyses and included all patients who were randomized and received at least one dose of study treatment. Patients in the SAF were grouped according to the treatment they actually received.

Analysis of Primary and secondary efficacy endpoint

The FAS population was used as the primary analysis population for all efficacy variables. Eligible patients were randomized and stratified by PSADT and use of osteoclast-targeted therapy. All efficacy analyses incorporated the stratification. Statistical testing was conducted to demonstrate the superiority of darolutamide vs. placebo in MFS. A stratified log-rank test was used to compare the darolutamide and placebo arms. The comparison was 2-sided at the 0.05 level of significance. For the primary efficacy endpoint, no formal interim analysis was planned.

Sensitivity analyses were conducted to assess the robustness of the results of the primary analysis of the MFS endpoint. The following sensitivity analyses were performed for MFS in the FAS: (1) censoring patients who died before documented metastasis; (2) considering all prohibited new treatment that started prior to documented metastasis as an event; (3) using stratification data from the case report from (CRF); (4) without including stratification factors in the model; (5) using MFS data based on investigator assessment; (6) considering all deaths independent of time of occurrence as MFS events; (7) using the event at the date of the first post-baseline scan with metastasis instead of event at randomization, for patients with baseline metastasis. If no metastasis was documented in post baseline scans, the patient was censored at the last available scan date. In case the patient did not have any post-baseline scans, the patient was censored at randomization. (8) excluding patients with the primary reason for permanent discontinuation of study treatment of "judgment of investigator" or "personal reason", and without MFS events (post-hoc analysis)

Sensitivity analyses 1-7 were also performed for MFS with baseline metastasis censored at randomization date. Different MFS censoring rules were to be used for the primary and secondary analyses of MFS for the United States and outside of the United States. For submissions outside of the United States the analysis with baseline metastasis censored (censored at date of randomization) was to be considered as primary analysis and the analysis with baseline metastasis as event (event at date of randomization) was to be considered as secondary analysis.

Key secondary efficacy endpoints were analysed in the FAS, and were tested hierarchically in the following order only if the primary endpoint MFS was significant: (1) Overall survival (OS), (2) Time to pain progression (TPP), (3) Time to initiation of first cytotoxic chemotherapy for prostate cancer (CYTOC), (4) Time to first symptomatic skeletal event (SSE). All secondary endpoints OS, PP, CYTOC and SSE were to be tested sequentially two times, in case the previous endpoint in the hierarchical order was significant. The first test for statistical significance was to occur at the time of the MFS analysis and the final test for statistical significance was to occur when approximately 240 OS events have been observed.

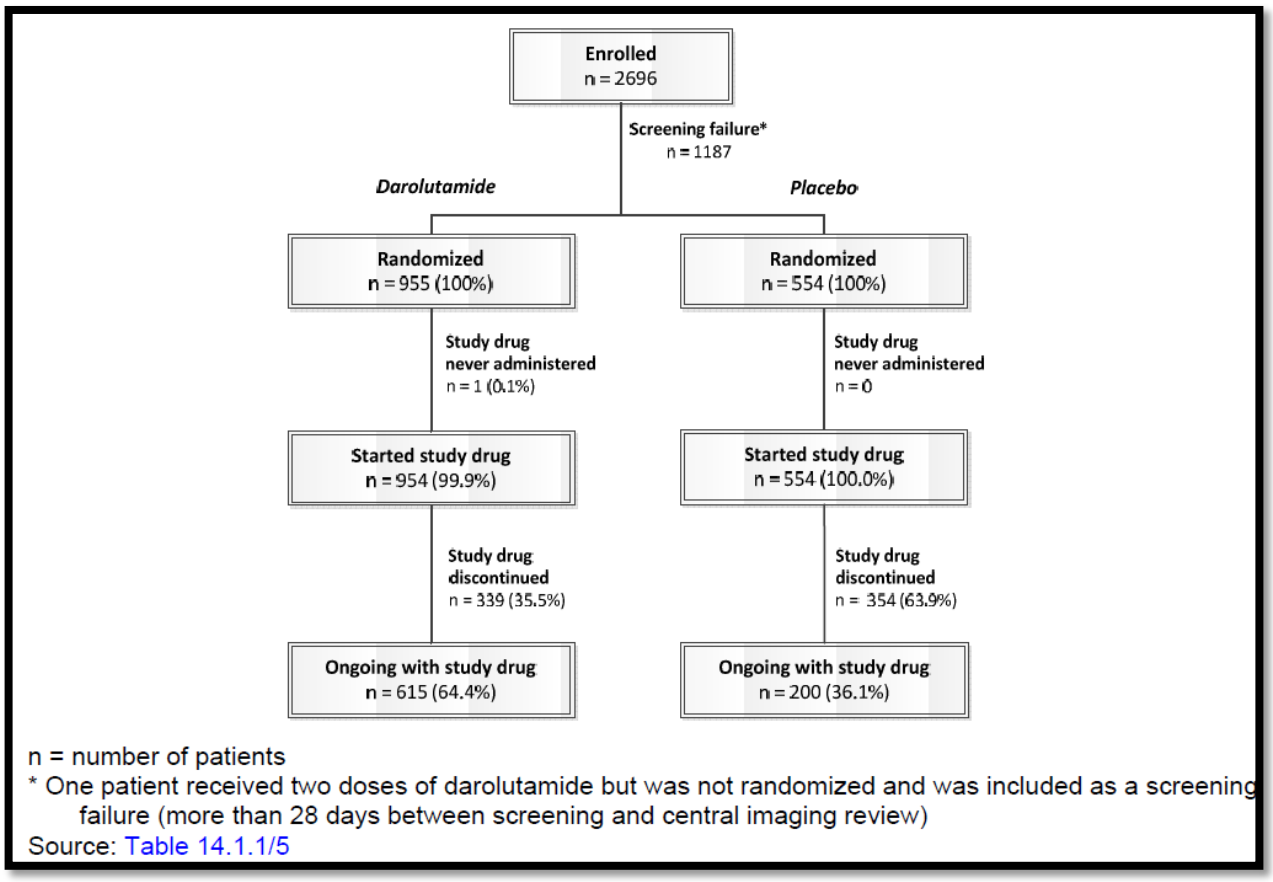
Regarding overall survival, patients not known to have died were censored at their last date of being known to be alive or at the database cut-off date, whichever came first. Patients lost to follow-up without contact after randomization were to be censored on the date of randomization.

PFS and time to PSA progression were analysed with the same methods as the primary variable MFS. PSA response rate was compared between treatment groups using a Cochran-Mantel-Haenszel test, adjusting for the same stratification factors as for the primary endpoint MFS.

For the PRO analyses, statistical tests were performed with a 2-sided type I error of 5%.

Results

Participant flow



n = number of patients
* One patient received two doses of darolutamide but was not randomized and was included as a screening failure (more than 28 days between screening and central imaging review)
Source: Table 14.1.1/5

Recruitment

The first patient, first visit was 12 September 2014 and the last patient, last visit: 3 September 2018 (cut-off date for the primary analysis); The study is still ongoing in terms of treatment and for follow up with the open label part having commenced in October 2018.

Conduct of the study

Protocol amendments

The original protocol, Version 1.0, was dated 10 March 2014. There were 3 major protocol amendments during the study which occurred prior to the primary analysis.

First protocol amendment (Protocol amendment 1, Version 2.0, dated 24 November 2014)

PFS was added as an additional endpoint during the first protocol amendment to capture the development of local regional LN soft tissue metastasis.

Soft tissue progression was clarified to exclude progression in lymph nodes in the pelvis below the aortic bifurcation which is more consistent with loco-regional progression and will not be defined as metastases. Patients with new pathologic lymph nodes identified in the pelvis below the aortic bifurcation could continue study treatment.

Eligibility related to PSA was amended to allow patients with CRPC defined as 3 rising PSA values at least 1 week apart during ADT to enter the study.

Second protocol amendment (Version 3.0, dated 19 July 2016)

The entry criteria were clarified in terms of CRPC definition and PSADT. Entry criteria was updated to clarify the inclusion criteria the required PSA value at screening of ≥2 ng/ml is required.

The time periods for detecting metastases by blinded central reading or a metastatic disease were specified.

Detection of all new suspected metastases on CT/MRI scan at soft tissues/visceral level should be confirmed by central review as is done for bone lesions.

Third protocol amendment (Version 4.0, dated 26 February 2018)

The option of an open label part of the study after the primary analysis with a positive benefit/risk was submitted during this amendment to allow patients in the placebo arm to cross over to receive darolutamide. Patients would still be followed up as per the blinded part with imaging every 16 weeks but only have local radiological imaging review.

Protocol deviations

Table 13: Number of patients with protocol deviations (FAS)

	Darolutamide N=955 n (%)	Placebo N=554 n (%)
Total – any type	**651/955 (68.2%)**	**403/955 (72.7%)**
Major	**1 (0.1%)**	**0**
Treatment deviations [a]	1/1 (100%)	0 (0%)
Important	**650/955 (68.1%)**	**403/955 (72.7%)**
Inclusion/exclusion criteria not met but patient entered treatment [b]	24/650 (3.7%)	10/403 (2.5%)
Randomization errors [b]	47/650 (7.2%)	36/403 (8.9%)
Treatment deviations [b]	20/650 (3.1%)	21/403 (5.2%)
Time schedule deviations [b]	1/650 (0.2%)	1/403 (0.2%)
Procedure deviations [b]	567/650 (87.2%)	356/403 (88.3%)
Prohibited concomitant treatment [b]	17/650 (2.6%)	25/403 (6.2%)
Failure to continue GnRH [b]	18/650 (2.8%)	9/403 (2.2%)
Incorrect/delayed ICF [b]	169/650 (26.0%)	91/403 (22.6%)
Blind broken (potential or actual) [b]	2/650 (0.3%)	3/403 (0.7%)
GCP breach [b]	25/650 (3.8%)	15/403 (3.7%)
Drug storage, handling, return process [b]	3/650 (0.5%)	4/403 (1.0%)
IRB/IEC requirement non-compliance [b]	1/650 (0.2%)	0/403 (0%)
Incorrect/delayed ancillary ICF [b]	32/650 (4.9%)	21/403 (5.2%)

Deviations from the pre-specified statistical analysis plan in the CSR

The definition of PSA progression as per SAP v.4.2 (defined according to the consensus guidelines of the PCWG2) was updated to achieve consistency with the relevant guidelines.

The analysis where baseline metastasis according to independent efficacy review is considered as an event was presented as the primary MFS analysis for the US and non US-submission while the SAP v4.2 stated that for submissions outside of the US the analysis with baseline metastasis censored at date of randomization would be considered the primary MFS analysis.

Baseline data

Table 14: Demographic and baseline disease characteristics of study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Age (years)		
n	955	554
Mean	73.9	73.2
StD	7.8	8.2
Min	48	50
Median	74.0	74.0
Max	95	92
Age group (years), n (%)		
<65	113 (11.8%)	84 (15.2%)
65-74	373 (39.1%)	216 (39.0%)
75-84	384 (40.2%)	209 (37.7%)
≥85	85 (8.9%)	45 (8.1%)
Race, n (%)		
Missing [a]	36 (3.8%)	19 (3.4%)
Asian	122 (12.8%)	71 (12.8%)
Black or African American	28 (2.9%)	24 (4.3%)
Other	9 (0.9%)	6 (1.1%)
White	760 (79.6%)	434 (78.3%)
Ethnicity, n (%)		
Not reported [a]	923 (96.6%)	539 (97.3%)
Hispanic or Latino	32 (3.4%)	15 (2.7%)
Geographical region, n (%)		
North America	108 (11.3%)	76 (13.7%)
Asia Pacific	119 (12.5%)	67 (12.1%)
ROW [b]	728 (76.2%)	411 (74.2%)

FAS = Full analysis set; Max = maximum; Min = minimum; N = Total number of patients (100%); n = Number of patients with event; ROW = Rest of the world; StD = Standard deviation; UK = United Kingdom.

a: Race was not collected if ethnicity was documented as "Hispanic or Latino". Data collection for race and ethnicity was not permitted in some countries, e.g. France.

b: ROW comprises Argentina, Austria, Australia, Belarus, Belgium, Brazil, Bulgaria, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Latvia, Lithuania, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Turkey, Ukraine and UK.

Source: Module 5.3.5.1, Report PH-39723, Table 14.1.1/19

	Darolutamide N = 955	Placebo N = 554
PSA central laboratory (ng/mL)		
Mean	18.651	19.755
StD	37.198	45.171
Min	0.31	1.46
Median	9.030	9.670
Max	858.30	885.21
Categories, n (%)		
≤10 ng/mL	508 (53.2%)	285 (51.4%)
>10 to ≤20 ng/mL	215 (22.5%)	122 (22.0%)
>20 ng/mL	232 (24.3%)	147 (26.5%)
Baseline value of PSADT [a], n (%)		
≤6 months	669 (70.1%)	371 (67.0%)
>6 months	286 (29.9%)	183 (33.0%)
PSADT (months) [b]		
N	955	554
Mean	4.8425	4.8876
StD	2.3555	2.2755
Min	0.744	0.662
Median	4.3890	4.6500
Max	10.991	13.194
Baseline osteoclast-targeted therapy [c], n (%)		
No	919 (96.2%)	526 (94.9%)
Yes	36 (3.8%)	28 (5.1%)
ECOG PS, n (%)		
0	650 (68.1%)	391 (70.6%)
1	305 (31.9%)	163 (29.4%)
Gleason total score at initial diagnosis (factor1+factor2), n (%)		
Missing	27 (2.8%)	17 (3.1%)
<7	217 (22.7%)	142 (25.6%)
≥7	711 (74.5%)	395 (71.3%)
Primary tumour classification at initial diagnosis, n (%)		
Missing [d]	26 (2.7%)	15 (2.7%)
T1 Clinically inapparent tumour neither palpable not visible by imaging	19 (2.0%)	13 (2.3%)
T1a Tumour incidental histological finding in >5% of tissue resected	5 (0.5%)	0
T1b Tumour incidental histological finding in >5% of tissue resected	9 (0.9%)	1 (0.2%)
T1c Tumour identified by needle biopsy	99 (10.4%)	53 (9.6%)
T2 Tumour confined within prostate	110 (11.5%)	58 (10.5%)
T2a Tumour involves = one-half of one lobe	32 (3.4%)	27 (4.9%)
T2b Tumour involves > one-half of one lobe but not both lobes	55 (5.8%)	38 (6.9%)
T2c Tumour involves both lobes	97 (10.2%)	72 (13.0%)
T3 Tumour extends through the prostate capsule	172 (18.0%)	87 (15.7%)
T3a Extracapsular extension (unilateral or bilateral)	113 (11.8%)	49 (8.8%)
T3b Tumour invades seminal vesicle(s)	130 (13.6%)	80 (14.4%)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles such as external	42 (4.4%)	26 (4.7%)
TX Primary tumour cannot be assessed	46 (4.8%)	35 (6.3%)

	Darolutamide N = 955	Placebo N = 554
Baseline presence of regional pathological lymph nodes by central imaging review, n (%) [e]		
No	792 (82.9%)	396 (71.5%)
Yes	163 (17.1%)	158 (28.5%)
Number of prior hormonal therapies [f]		
1	177 (18.5%)	103 (18.6%)
≥2	727 (76.1%)	420 (75.8%)
Not applicable	51 (5.3%)	31 (5.6%)
Time since becoming castration-resistant to start of study treatment (months)		
n	954	553
Mean	11.7117	12.7736
StD	19.0278	22.8391
Min	0.033	0.099
Median	5.5355	5.9461
Max	170.368	233.016
Time since initial diagnosis to start of study treatment (months) [g]		
n	950	548
Mean	94.75	94.89
StD	55.33	59.44
Min	2.6	0.5
Median	86.15	84.23
Max	337.5	344.7
Time from start of first prior antiandrogen (AR inhibitors [h]) to start of study treatment (months)		
n	633	349
Mean	61.956	64.276
StD	45.752	48.129
Min	2.23	2.96
Median	51.150	50.820
Max	232.82	229.57
Time from start of first prior ADT [i] to start of study treatment (months)		
n	953	551
Mean	76.138	75.981
StD	56.124	54.170
Min	0.92	2.92
Median	64.160	61.860
Max	644.35	386.63

	Darolutamide N = 955	Placebo N = 554

ADT = Androgen deprivation therapy; AR = Androgen receptor; ATC = Anatomical Therapeutic Chemical classification system; CRF = Case report form; ECOG PS = Eastern Cooperative Oncology Group performance status; FAS = Full analysis set; GnRH = Gonadotropin-releasing hormone; Max = Maximum, Min = Minimum; N = Total number of patients (100%); n = Number of patients with event; PCWG2 = Prostate cancer Clinical Trials Working Group 2; PSA = Prostate-specific antigen; PSADT = Prostate-specific antigen doubling time; SAP = Statistical analysis plan; StD = Standard deviation.

a: Values based on CRF data.

b: For 14 patients, the time interval for collection of PSA samples for calculation of PSADT was between 12 and 14 months, which was slightly beyond the timelines required by PCWG2 criteria but has no meaningful impact on the results of the study.

c: Values based on CRF data. Patients receiving osteoclast-targeted therapy to prevent skeletal related events within 12 weeks before randomization were excluded per protocol. Patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis prior to study entry could continue treatment at the same dose and schedule.

d: Missing: for two patients tumour classification was not made at initial diagnosis, for one patient the classification was reported as T3c, and for all others the original records were not available to the sites (data on file).

e: Local assessment of regional lymph node classification is available in Module 5.3.5.1, Report PH-39723, Table 14.1.1/20.

f: Not applicable = patients who underwent surgical castration were not required to have been/be treated with hormonal drug therapy. For the definition (ATC codes) of hormonal therapies, see Module 5.3.5.1, Report PH-39723, Section 16.1.9 SAP v.4.2, Section 9.13.

g: The earlier date between the clinical stage date and the Gleason assessment date was considered as the initial diagnosis date.

h: For the definition (ATC codes) of AR inhibitors, see Module 5.3.5.1, Report PH-39723, Section 16.1.9 SAP v.4.2, Section 9.11.

i: Prior ADT is defined by GnRH agonist/antagonist, orchiectomy, antiandrogens (AR inhibitors). For the definitions (ATC codes) of AR inhibitors and GnRH agonists/antagonists, see Module 5.3.5.1, Report PH-39723, Section 16.1.9 SAP v.4.2, Section 9.11 and Section 9.12, respectively.

Notes: Time variable is missing if only year was documented.

Baseline data are taken from the non-missing observation before or on the first date of study drug intake. Baseline values for PSADT and osteoclast-targeted therapy collected on CRF are based on randomization date.

Source: Module 5.3.5.1, Report PH-39723, Table 14.1.1/20

At baseline reviewers were instructed to document seemingly abnormal lymph nodes that were ≥15 mm in the short axis according to RECIST 1.1 and follow them for regional progression. Therefore, lymph nodes were regarded as pathological if ≥15 mm and were included in the baseline regional LN count.

The majority of patients had no regional pathological LNs at baseline. However, on retrospective/post hoc analysis of the baseline imaging during the efficacy review (performed by a separate group of independent central radiologists), 5.2% of patients in the darolutamide arm and 7.0% of patients in the placebo arm were retrospectively classified with metastases despite distant metastasis listed in the exclusion criteria.

Patients with a medical history of seizure were allowed to enter the study. There were 12 patients (0.21%) enrolled on the darolutamide arm with a history of seizure.

Table 15: Summary of prior primary therapeutic procedure for prostate cancer in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955 n (%)	Placebo N = 554 n (%)
Prior procedures (as primary therapy)	**954 (99.9%)**	**554 (100.0%)**
Active surveillance	12 (1.3%)	7 (1.3%)
Chemical castration	403 (42.2%)	252 (45.5%)
Orchiectomy	91 (9.5%)	50 (9.0%)
Other, specify	32 (3.4%)	22 (4.0%)
Prostatectomy	239 (25.0%)	134 (24.2%)
Radiotherapy	177 (18.5%)	89 (16.1%)

FAS = Full analysis set; N = Total number of patients (100%); n = Number of patients with event.
Note: Patient may have more than one entry.

Table 16: Number of subjects with at least one prior radiotherapy (full analysis set)

Prior Radiotherapy	Darolutamide N=955 (100%)	Placebo N=554 (100%)	Total N=1509 (100%)
No	465 (48.7%)	288 (52.0%)	753 (49.9%)
Yes	490 (51.3%)	266 (48.0%)	756 (50.1%)

Numbers analysed

Table 17: Patient disposition at the time of database cut-off 3 September 2018

Patient disposition		
Enrolled [a]	2696	
Screening failures [b]	1187	
	Darolutamide	**Placebo**
Randomized (N = 1509; included in FAS)	**955 (100%)**	**554 (100%)**
Study drug never administered	1/955 (0.1%)	0/554
Started treatment (N = 1508; included in SAF)	954/955 (99.9%)	554/554 (100.0%)
Ongoing with treatment (as of the cut-off date)	**615/955 (64.4%)**	**200/554 (36.1%)**
Discontinued study treatment	**339/955 (35.5%)**	**354/554 (63.9%)**
Entered follow-up [c]	**291/955 (30.5%)**	**332/554 (59.9%)**
Ongoing with follow-up [d]	117/291 (40.2%)	169/332 (50.9%)
Discontinued follow-up [d]	174/291 (59.8%)	163/332 (49.1%)

AE = adverse event; FAS = full analysis set; N = total number of patients; SAF = safety analysis set
a: The number of patients enrolled is the number of patients who signed informed consent. Re-screened patients were only considered once (last enrollment captured).
b: One patient received two doses of darolutamide but was not randomized and was included as a screening failure (more than 28 days between screening and central imaging review), and therefore was not included in any analysis set.
c: Patients with an end of treatment visit and/or follow-up visit and/or documented reason of discontinuation of follow-up were considered to have entered follow-up. Not all of the patients performed the first follow-up visit.
d: Percentages of patients who were ongoing with follow-up and who discontinued follow-up were manually calculated by treatment arm from the number of patients who entered follow-up.

Table 18: Summary of discontinuation of treatment in study 17712 (ARAMIS) (FAS)

	Darolutamide		Placebo	
Number of patients (%)	Total N = 955 n (%)	Discontinued treatment N = 339 [a] n (%)	Total N = 554 n (%)	Discontinued treatment N = 354 [a] n (%)
Discontinued study treatment, primary reason:	**339 (35.5%)**	**339 (100%)**	**354 (63.9%)**	**354 (100%)**
Adverse event	86 (9.0%)	86 (25.4%)	47 (8.5%)	47 (13.3%)
Confirmed metastasis	112 (11.7%)	112 (33.0%)	129 (23.3%)	129 (36.4%)
Judgment of the investigator	54 (5.7%)	54 (15.9%)	91 (16.4%)	91 (25.7%)
Other	6 (0.6%)	6 (1.8%)	2 (0.4%)	2 (0.6%)
Personal reason	68 (7.1%)	68 (20.1%)	78 (14.1%)	78 (22.0%)
Protocol deviation	13 (1.4%)	13 (3.8%)	7 (1.3%)	7 (2.0%)

FAS = Full analysis set; N = Total number of patients (100%); n = Number of patients with event.
a: Percentages in this column were manually calculated from the number of patients in the treatment arm who discontinued study treatment.

The most frequent personal reason for treatment discontinuation was consent withdrawal while the judgement of the investigator was mainly due to disease progression (clinical or PSA increase based on local assessment).

Outcomes and estimation

Primary endpoint: MFS

Table 19: Description of MFS events in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955 n (%)	Placebo N = 554 n (%)
Any event [a]	**221/955 (23.1%)**	**216/554 (39.0%)**
Metastasis post baseline [b]	**130/221 (58.8%)**	**158/216 (73.1%)**
Bone [c]	60/130 (46.2%)	62/158 (39.2%)
Distant lymph nodes [c]	41/130 (31.5%)	63/158 (39.9%)
Distant lymph nodes, and bone [c]	17/130 (13.1%)	22/158 (13.9%)
Distant lymph nodes, and visceral and/or soft tissue [c]	2/130 (1.5%)	4/158 (2.5%)
Distant lymph nodes, and visceral and/or soft tissue, and bone [c]	0	1/158 (0.6%)
Visceral and/or soft tissue [c]	9/130 (6.9%)	4/158 (2.5%)
Visceral and/or soft tissue, and bone [c]	1/130 (0.8%)	2/158 (1.3%)
Metastasis at baseline [b]	**50/221 (22.6%)**	**39/216 (18.1%)**
Bone [d]	34/50 (68.0%)	24/39 (61.5%)
Distant lymph nodes [d]	10/50 (20.0%)	8/39 (20.5%)
Distant lymph nodes, and bone [d]	3/50 (6.0%)	4/39 (10.3%)
Distant lymph nodes, and visceral and/or soft tissue [d]	1/50 (2.0%)	0
Distant lymph nodes, and visceral and/or soft tissue, and bone [d]	0	0
Visceral and/or soft tissue [d]	1/50 (2.0%)	3/39 (7.7%)
Visceral and/or soft tissue, and bone [d]	1/50 (2.0%)	0
Death [b]	**41/221 (18.6%)**	**19/216 (8.8%)**

FAS = Full analysis set; MFS = Metastasis-free survival; N = Total number of patients (100%); n = Number of patients with event.
a: Patients with documented metastases at baseline were considered to have an MFS event at randomization.
b: Percentages for the type of MFS event were manually calculated by treatment arm from the number of patients with event.
c: Percentages for the type of metastasis were calculated by treatment arm from the number of patients with metastasis.
d: Percentages for the type of baseline metastasis were calculated by treatment arm from the number of patients with baseline metastasis.

Table 20: Metastasis-free survival analysis with baseline metastasis non-censored in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	221 (23.1%)	216 (39.0%)
Number (%) of patients censored	734 (76.9%)	338 (61.0%)
MFS (months)		
Median [95% CI]	40.37 [34.33; A]	18.43 [15.51; 22.34]
Range (including censored values)	(0.03 - 44.28**)	(0.03 - 36.89)
Range (without censored values)	(0.03 - 40.51)	(0.03 - 36.89)
4-month event-free rate [95% CI]	0.916 [0.898; 0.934]	0.820 [0.786; 0.853]
8-month event-free rate [95% CI]	0.879 [0.858; 0.901]	0.720 [0.679; 0.761]
12-month event-free rate [95% CI]	0.825 [0.799; 0.851]	0.635 [0.588; 0.681]
24-month event-free rate [95% CI]	0.698 [0.658; 0.738]	0.415 [0.351; 0.480]
36-month event-free rate [95% CI]	0.543 [0.466; 0.620]	0.268 [0.160; 0.375]
48-month event-free rate [95% CI]	A [A; A]	0.000 [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [b]	0.413 [0.341; 0.500]	
Two sided p-value from log-rank test	<0.000001	

A = Value cannot be estimated; CI = Confidence interval; FAS = Full analysis set; MFS = Metastasis-free survival; N = Total number of patients (100%); PSADT = Prostate-specific antigen doubling time.

** Censored observation.

a: Patients with documented metastases at baseline (50 patients in the darolutamide arm, and 39 patients in the placebo arm, see Table 3–16) were considered to have an MFS event at randomization.

b: A hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

Note: Median and 95% CIs computed using Kaplan-Meier estimates.

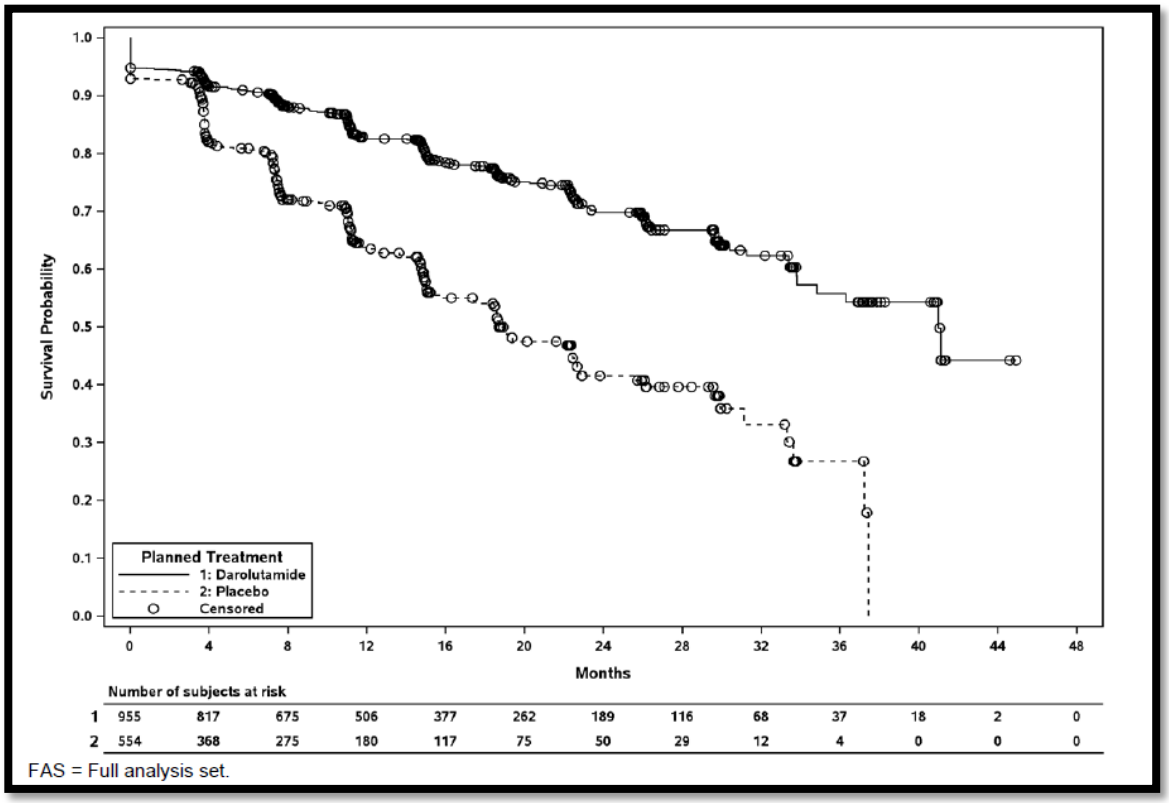


Figure 2: Kaplan-Meier curves of metastatis-free survival with baseline metastasis non-censored in study 17712 (ARAMIS) (FAS)

Secondary endpoints

Overall Survival

Table 21: Overall survival in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	78 (8.2%) [a]	58 (10.5%)
Number (%) of patients censored	877 (91.8%)	496 (89.5%)
OS (months)		
Median [95% CI]	A [44.45; A]	A [A; A]
Range (including censored values)	(0.07** - 46.02**)	(0.1** - 45.57**)
Range (without censored values)	(0.85 - 44.45)	(3.15 - 34.53)
4-month survival rate [95% CI]	0.993 [0.987; 0.998]	0.994 [0.988; 1.000]
8-month survival rate [95% CI]	0.983 [0.975; 0.991]	0.985 [0.974; 0.995]
12-month survival rate [95% CI]	0.961 [0.948; 0.974]	0.966 [0.950; 0.983]
24-month survival rate [95% CI]	0.900 [0.875; 0.925]	0.855 [0.814; 0.897]
36-month survival rate [95% CI]	0.828 [0.779; 0.877]	0.728 [0.647; 0.809]
48-month survival rate [95% CI]	A [A; A]	A [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [b]	0.706 [0.501; 0.994]	
Two sided p-value from log-rank test	0.045210	

A = Value cannot be estimated; CI = Confidence interval; FAS = Full analysis set; N = Total number of patients (100%); OS = Overall survival; PSADT = Prostate-specific antigen doubling time.

** Censored observation.

a: For 1 patient in the darolutamide arm, death was not considered an event for the OS analysis as only the year of death was reported and thus the time to event could not be calculated.

b: A hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and its 95% CI were based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

Median and 95% CIs were computed using Kaplan-Meier estimates.

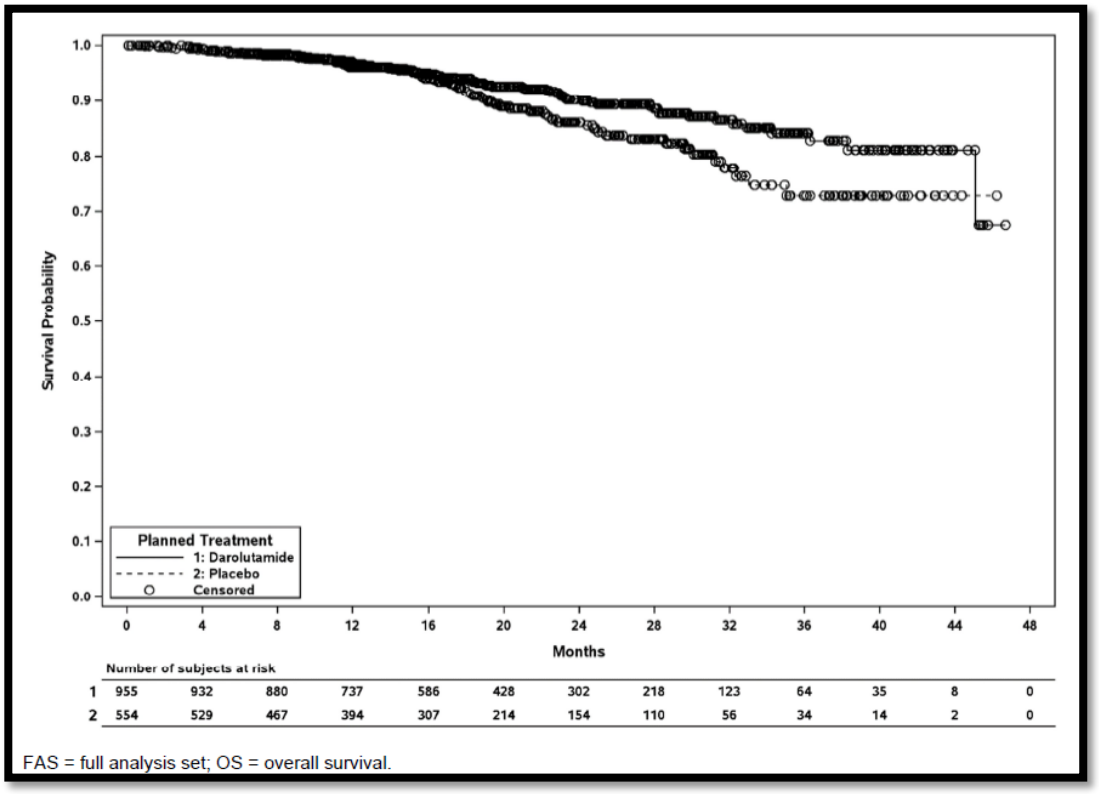


Figure 3: Kaplan-Meier curves of OS in study 17712 (ARAMIS) (FAS)

Time to pain progression

Table 22: Time to pain progression in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	251 (26.3%)	178 (32.1%)
Number (%) of patients censored	704 (73.7%)	376 (67.9%)
Time to pain progression (months)		
25th percentile [95% CI]	14.68 [11.10; 18.43]	8.94 [7.39; 11.07]
Median [95% CI]	40.31 [33.21; 41.20]	25.36 [19.09; 29.63]
75th percentile [95% CI]	41.20 [40.80; A]	A [32.79; A]
Range (including censored values)	(0.03** - 44.32**)	(0.03** - 40.51**)
Range (without censored values)	(2.1 - 41.2)	(2.76 - 32.79)
4-month event-free rate [95% CI]	0.909 [0.889; 0.928]	0.867 [0.837; 0.898]
8-month event-free rate [95% CI]	0.821 [0.795; 0.848]	0.754 [0.714; 0.795]
12-month event-free rate [95% CI]	0.760 [0.729; 0.790]	0.686 [0.641; 0.732]
24-month event-free rate [95% CI]	0.646 [0.604; 0.687]	0.504 [0.441; 0.567]
36-month event-free rate [95% CI]	0.534 [0.468; 0.601]	0.323 [0.216; 0.430]
48-month event-free rate [95% CI]	A [A; A]	A [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [a]	0.647 [0.533; 0.785]	
Two sided p-value from log-rank test	0.000008	

A = value cannot be estimated; CI = confidence interval; FAS = full analysis set; N = total number of patients (100%); PSADT = prostate-specific antigen doubling time

** Censored observation

a: A hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

Note: Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.

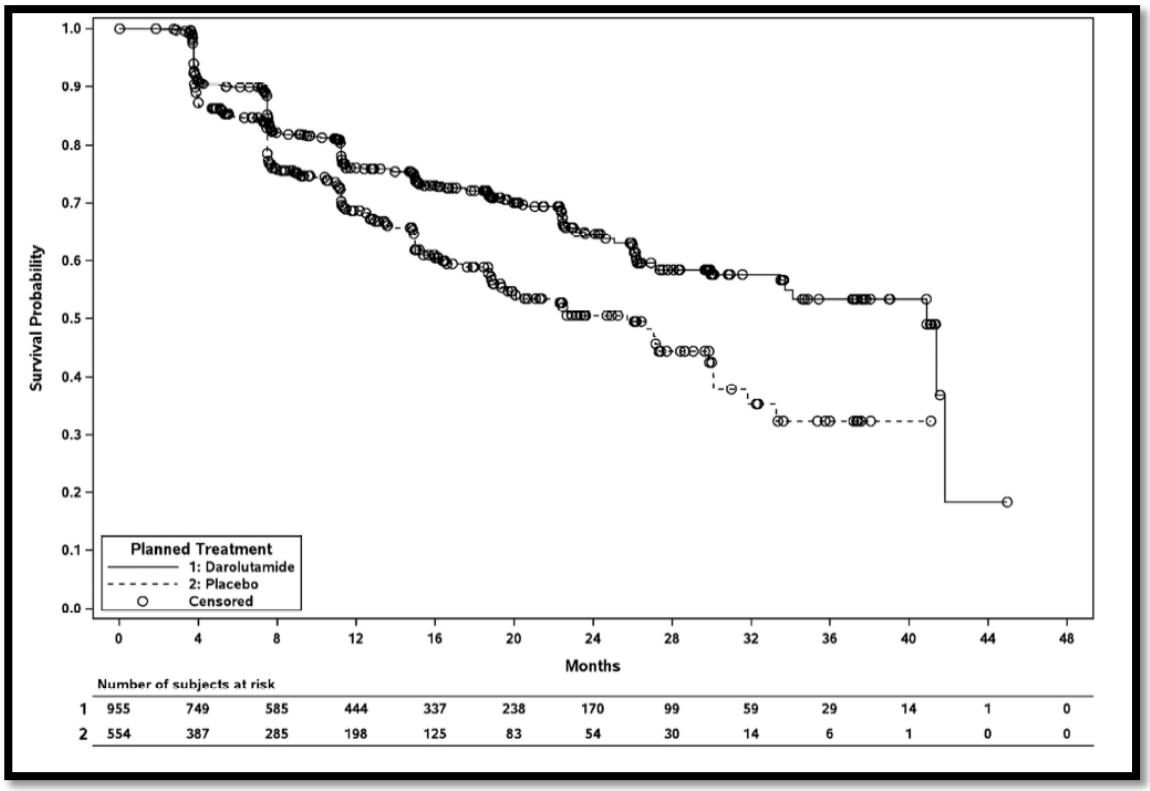


Figure 4: Kaplan-Meier curves of time to pain progression in study 17712 (ARAMIS) (FAS)

Time to initiation of first cytotoxic chemotherapy for prostate cancer

Table 23: Time to initiation of first cytotoxic chemotherapy for prostate cancer in study 17712 (ARAMIS) (FAS)

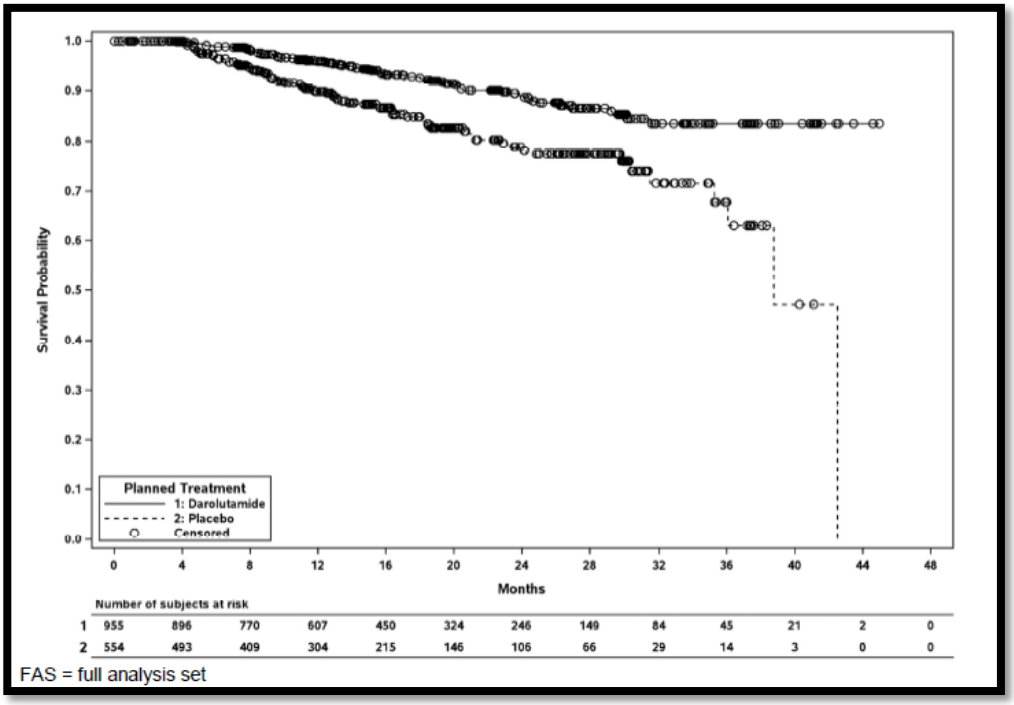
	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	73 (7.6%)	79 (14.3%)
Number (%) of patients censored	882 (92.4%)	475 (85.7%)
Time to initiation of first cytotoxic chemotherapy (months)		
25th percentile [95% CI]	A [A; A]	29.93 [22.44; 35.55]
Median [95% CI]	A [A; A]	38.21 [35.55; 41.89]
75th percentile [95% CI]	A [A; A]	41.89 [38.21; 41.89]
Range (including censored values)	(0.03** - 44.32**)	(0.03** - 41.89)
Range (without censored values)	(4.01 - 31.04)	(3.58 - 41.89)
4-month event-free rate [95% CI]	1.000 [1.000; 1.000]	0.996 [0.991; 1.000]
8-month event-free rate [95% CI]	0.979 [0.969; 0.988]	0.945 [0.925; 0.966]
12-month event-free rate [95% CI]	0.960 [0.947; 0.974]	0.898 [0.870; 0.927]
24-month event-free rate [95% CI]	0.887 [0.858; 0.915]	0.773 [0.720; 0.825]
36-month event-free rate [95% CI]	0.835 [0.790; 0.879]	0.629 [0.496; 0.763]
48-month event-free rate [95% CI]	A [A; A]	0.000 [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [a]	0.433 [0.314; 0.595]	
Two sided p-value from log-rank test	<0.000001	

A = value cannot be estimated; CI = confidence interval; FAS = full analysis set; N = total number of patients (100%); PSADT = prostate-specific antigen doubling time

** Censored observation

a: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and its 95% CI were based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

Note: Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.



FAS = full analysis set

Figure 5: Kaplan-Meier curves of time to initiation of first cytotoxic chemotherapy in study 17712 (ARAMIS) (FAS)

Time to first symptomatic skeletal event (SSE)

Table 24: Time to first symptomatic skeletal event (SSE) in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	16/955 (1.7%)	18/554 (3.2%)
EBRT to relieve skeletal symptoms [a]	12/16 (75.0%)	11/18 (61.1%)
New symptomatic pathologic bone fracture [a]	2/16 (12.5%)	2/18 (11.1%)
Occurrence of spinal cord compression [a]	0/16 (0%)	3/18 (16.7%)
Tumor-related orthopedic surgical intervention [a]	2/16 (12.5%)	2/18 (11.1%)
Number (%) of patients censored	939/955 (98.3%)	536/554 (96.8%)
Time to first SSE (months)		
25th percentile [95% CI]	A [A; A]	A [38.21; A]
Median [95% CI]	A [A; A]	A [A; A]
75th percentile [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03** - 44.65**)	(0.03** - 42.38**)
Range (without censored values)	(1.58 - 34.2)	(2.33 - 38.21)
4-month event-free rate [95% CI]	0.999 [0.997; 1.000]	0.996 [0.991; 1.000]
8-month event-free rate [95% CI]	0.996 [0.991; 1.000]	0.992 [0.983; 1.000]
12-month event-free rate [95% CI]	0.993 [0.987; 0.999]	0.982 [0.969; 0.994]
24-month event-free rate [95% CI]	0.980 [0.968; 0.992]	0.948 [0.920; 0.976]
36-month event-free rate [95% CI]	0.940 [0.896; 0.984]	0.904 [0.834; 0.974]
48-month event-free rate [95% CI]	A [A; A]	A [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [b]	0.428 [0.218; 0.842]	
Two sided p-value from log-rank test	0.011262	

A = value cannot be estimated; CI = confidence interval; EBRT = external beam radiation therapy; FAS = full analysis set; N = total number of patients (100%); PSADT = prostate-specific antigen doubling time; SSE = symptomatic skeletal event

** Censored observation

a: Percentages for the type of SSE were manually calculated by treatment arm from the number of patients with event.

b: A hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

Note: Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.

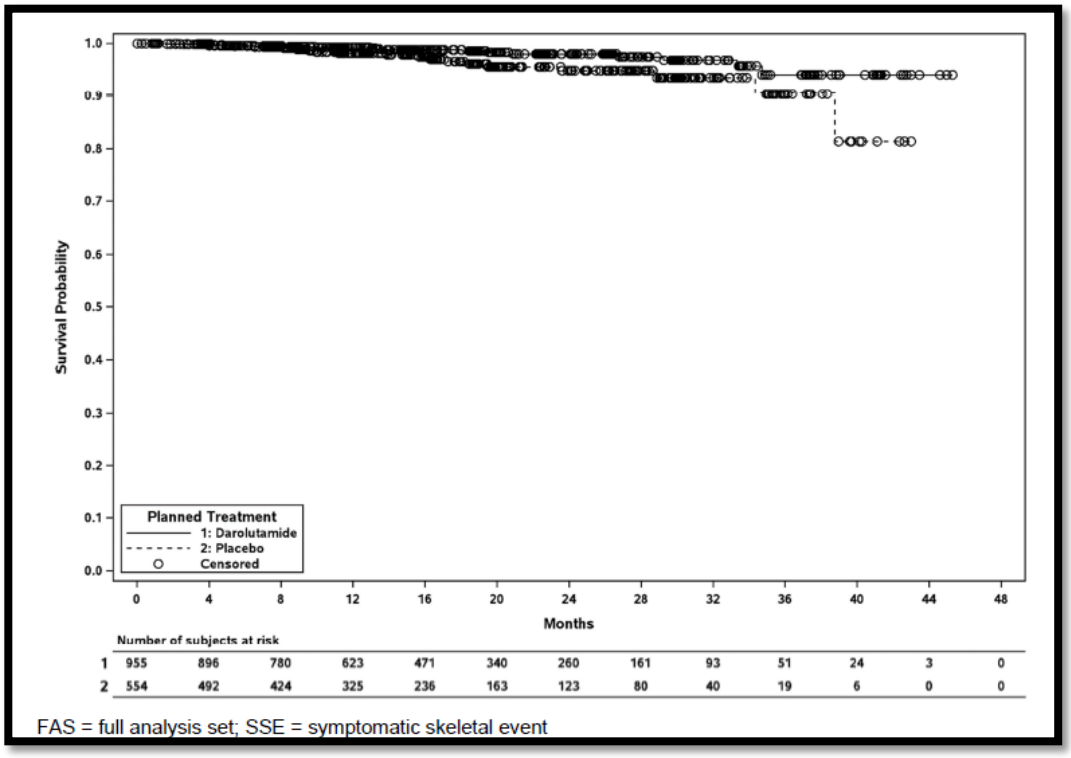


Figure 6: Kaplan-Meier curves of time to first symptomatic skeletal event (SSE) in study 17712 (ARAMIS) (FAS)

Additional endpoints

Progression-free survival

Table 25: PFS with baseline metastasis non-censored in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	255 (26.7%)	258 (46.6%)
Number (%) of patients censored	700 (73.3%)	296 (53.4%)
PFS (months)		
25th percentile [95% CI]	14.95 [14.62; 19.05]	3.91 [3.75; 7.19]
Median [95% CI]	36.83 [32.92; A]	14.82 [11.83; 18.43]
75th percentile [95% CI]	A [A; A]	32.82 [26.02; A]
Range (including censored values)	(0.03 - 44.28**)	(0.03 - 36.83**)
Range (without censored values)	(0.03 - 40.37)	(0.03 - 36.7)
4-month event-free rate [95% CI]	0.904 [0.885; 0.923]	0.747 [0.709; 0.785]
8-month event-free rate [95% CI]	0.857 [0.834; 0.880]	0.636 [0.593; 0.679]
12-month event-free rate [95% CI]	0.796 [0.769; 0.824]	0.547 [0.500; 0.595]
24-month event-free rate [95% CI]	0.651 [0.610; 0.692]	0.349 [0.288; 0.410]
36-month event-free rate [95% CI]	0.512 [0.441; 0.583]	0.226 [0.142; 0.310]
48-month event-free rate [95% CI]	A [A; A]	A [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [a]	0.380 [0.319; 0.454]	
Two sided p-value from log-rank test	<0.000001	

A = value cannot be estimated; CI = confidence interval; FAS = full analysis set; N = total number of patients (100%); PFS = progression-free survival; PSADT = prostate-specific antigen doubling time

** Censored observation

a: A hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

Note: Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.

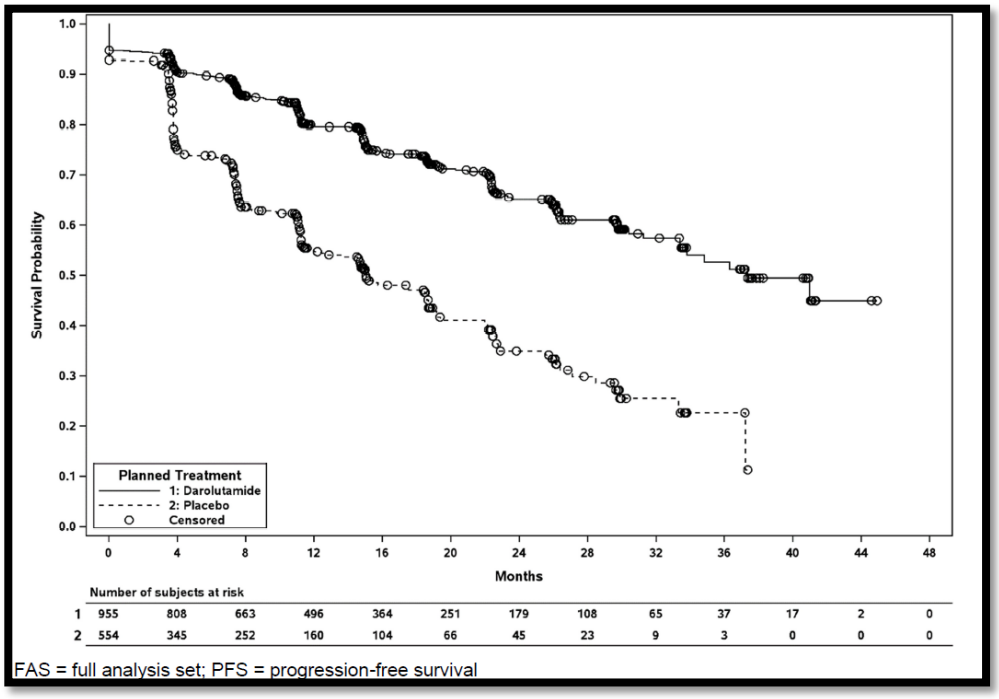


Figure 7: Kaplan-Meier curves of PFS with baseline metastasis non-censored in study 17712 (ARAMIS) (FAS)

Baseline metastasis censored PFS results were also in favour of the darolutamide arm; HR = 0.331; [95% CI: [0.273; 0.402]; p<0.000001].

Time to first prostate cancer-related invasive procedures

Table 26: Time to first prostate cancer-related invasive procedures in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	34 (3.6%)	44 (7.9%)
Number (%) of patients censored	921 (96.4%)	510 (92.1%)
Time to first prostate cancer-related invasive procedure (months)		
25th percentile [95% CI]	A [A; A]	A [34.20; A]
Median [95% CI]	A [A; A]	A [A; A]
75th percentile [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03** - 44.65**)	(0.03** - 42.38**)
Range (without censored values)	(1.08 - 32.82)	(0.43 - 34.2)
4-month event-free rate [95% CI]	0.996 [0.992; 1.000]	0.977 [0.964; 0.990]
8-month event-free rate [95% CI]	0.988 [0.980; 0.995]	0.960 [0.943; 0.977]
12-month event-free rate [95% CI]	0.976 [0.965; 0.986]	0.942 [0.921; 0.964]
24-month event-free rate [95% CI]	0.951 [0.932; 0.970]	0.883 [0.845; 0.921]
36-month event-free rate [95% CI]	0.919 [0.881; 0.956]	0.813 [0.733; 0.894]
48-month event-free rate [95% CI]	A [A; A]	A [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [a]	0.389 [0.248; 0.609]	
Two sided p-value from log-rank test	0.000020	

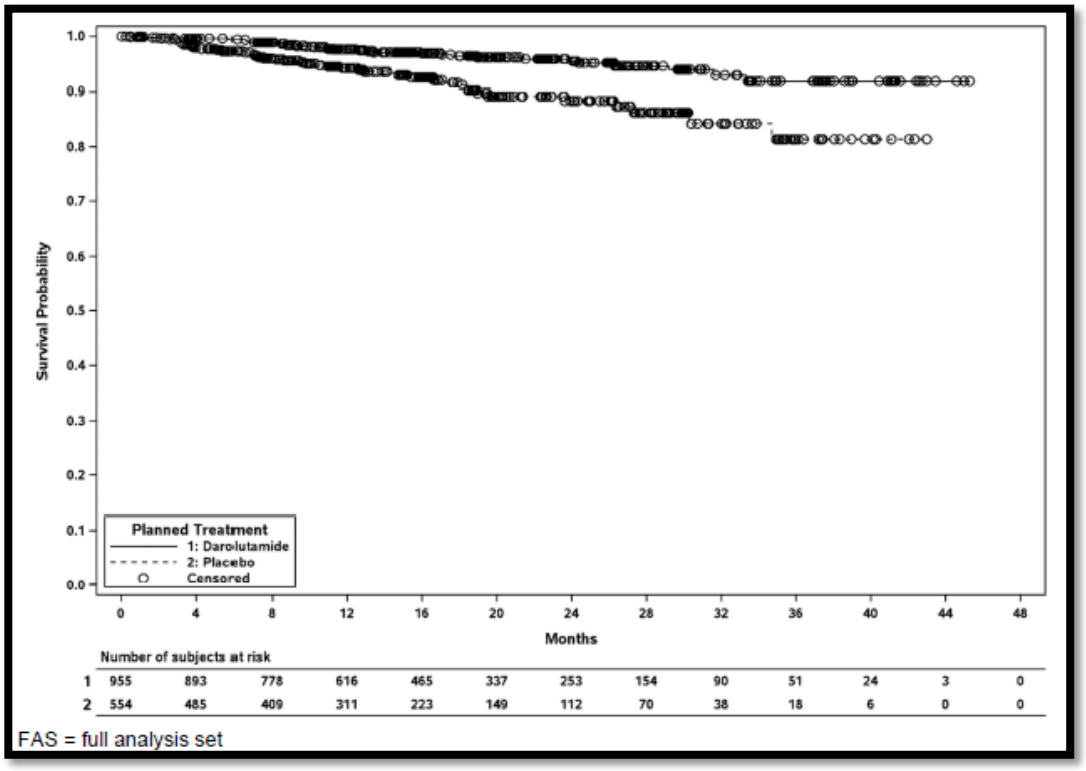
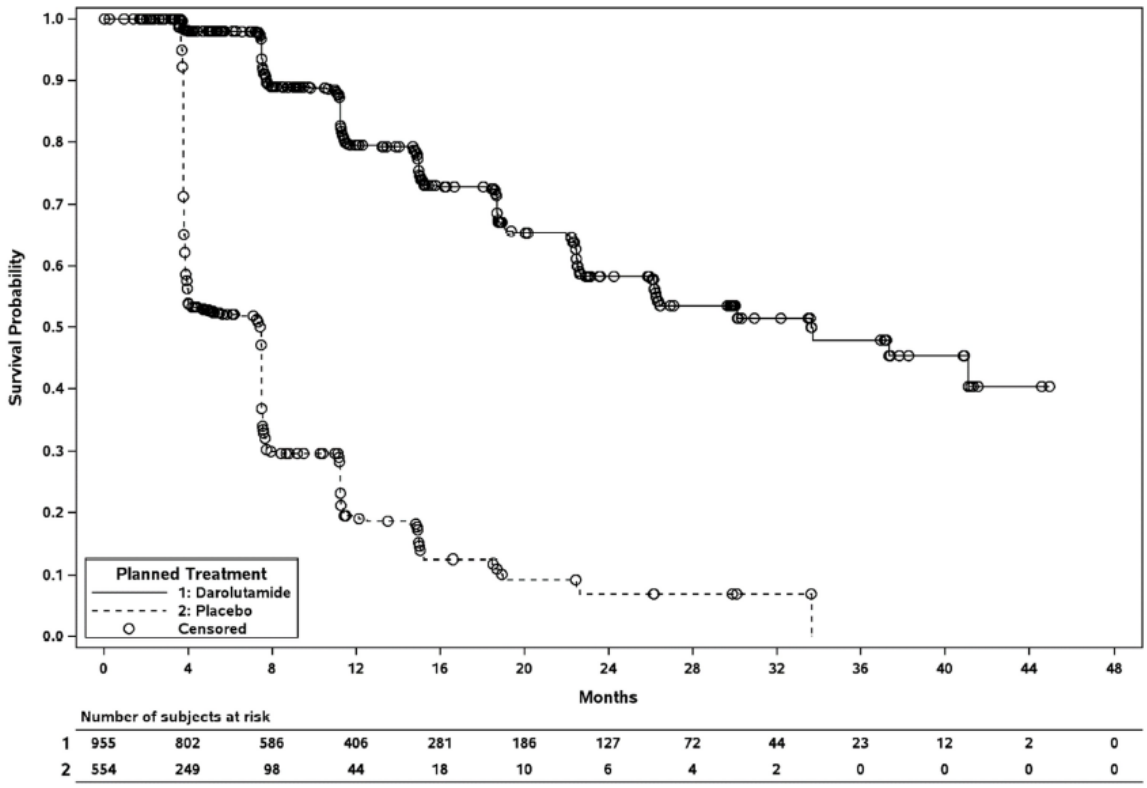


Figure 8: Kaplan-Meier curves of time to first prostate cancer-related invasive procedures in study 17712 (ARAMIS) (FAS)

Time to PSA Progression and Percent of patients with PSA response

The median PSA progression in the darolutamide arm was 33.15 months versus 7.33 months in the placebo arm with a HR of 0.130 [0.109; 0.156] favouring darolutamide. There was a smaller proportion of patients in the darolutamide arm (23.7%) compared to the placebo arm (66.4%) with PSA progression.



FAS = full analysis set; PSA = prostate-specific antigen
Source: Figure 14.2.3/5

Figure 9: Kaplan-Meier curves of time to PSA progression (FAS)

Patients receiving darolutamide in the ARAMIS study demonstrated a significantly higher confirmed PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 83.6% vs 7.6% (difference = 76%, p<0.000001).

Health-related QoL

The percent of patients with a deterioration of FACT-P total score at 16 weeks was similar in the darolutamide arm (17.5%; 95% CI: [15.1%; 20.0%]) compared to the placebo arm (21.1%; 95% CI: [17.8%; 24.8%]). The difference in deterioration rate was 3.45 (95% CI: [-0.72%; 7.62%], p=0.099804). The difference in deterioration rate was below the meaningfully important difference (MID) threshold of 10, and the results imply that HRQoL was similarly maintained up to 16 weeks between the treatment arms. At baseline, mean total scores were similar between the treatment arms. Small changes in mean values from baseline for the total score and subscores were observed in both treatment arms, but there were no clinically meaningful differences (MID of 3 for Physical Well Being, Social/Family Well Being, Emotional Well Being, Functional Well Being, Prostate Cancer Symptoms; MID of 7 for FACT-G total; MID of 10 for FACT-P total; MID of 9 for Trial Outcome Index) between the treatment arms at any of the time points.

The ANCOVA analyses of time-adjusted AUC showed that for all subscales the results favoured darolutamide (higher scores represent better HRQoL). Even though some results were statistically significant, none of the differences in LS means between the treatment arms crossed the MID thresholds, implying that HRQoL was similarly maintained throughout the study for the FACT-P total score and subscores.

At baseline, mean PCS subscale scores were similar between the treatment arms. General decreases in mean values from baseline for PCS subscale scores were observed in both treatment arms, but there were no clinically meaningful differences (MID = 3) between the treatment arms at any of the time points.

Deterioration in PCS subscore was observed for 61.8% of the patients in the darolutamide arm and 63.9% of the patients in the placebo arm. The times to deterioration in PCS subscore were longer in the darolutamide arm than in the placebo arm, with a median time to deterioration in PCS subscore of 11.07 months (95% CI: [11.04, 11.14]) in the darolutamide arm compared with 7.88 months (95% CI: [7.46, 11.07]) in the placebo arm, which is a benefit of 3.19 months for darolutamide14. A treatment effect in favour of darolutamide with respect to time to deterioration in PCS was observed, with a HR of 0.796 (95% CI: [0.697, 0.908]) and a two-sided p-value of 0.000517.

Completion rates of the EORTC-QLQ-PR25 were comparable between the treatment arms. The percent of patients with improvement of urinary symptoms was higher in the darolutamide arm (46.4%; 95% CI: [43.2%; 49.6%]) compared to the placebo arm (34.8%; 95% CI: [30.9%; 39.0%]), with a difference in in improvement rate of -11.35 (95% CI: [-16.44%; -6.26%], p=0.000018).

Changes in mean values for EORTC-QLQ-PR25 urinary symptoms scores over time favour darolutamide (higher scores represent greater symptom impact) at most time points.

At baseline, EORTC-QLQ-PR25 urinary symptoms scores were similar between the treatment arms. Changes in mean values from baseline for the urinary symptoms scores were observed in both treatment arms and favoured darolutamide, but there were no clinically meaningful differences (MID = 8) in the urinary symptoms score at any of the time points.

The urinary symptom score results favoured darolutamide and were statistically significant but were not clinically meaningful, as the difference in LS means between the treatment arms did not meet the MID threshold.

Worsening of urinary symptoms based on the EORTC-QLQ-PR25 questionnaire was observed for 43.6% of the patients in the darolutamide arm and 51.1% of the patients in the placebo arm. The times to worsening of urinary symptoms were longer in the darolutamide arm than in the placebo arm, with a median time of 14.78 months (95% CI: [14.52, 18.43]) in the darolutamide arm compared with 7.62 months (95% CI: [7.39, 11.04]) in the placebo arm, which is a benefit of 7.16 months for darolutamide. A treatment effect in favour of darolutamide with respect to time to worsening of urinary symptoms was observed with a HR of 0.619 (95% CI: [0.530, 0.721]) and a two-sided p-value of <0.000001.

Completion rates of the EQ-5D-3L were comparable between the treatment arms. The percent of patients with deterioration of EQ-5D-3L index score at 16 weeks was similar in the darolutamide arm (21.9%; 95% CI: [19.3%; 24.6%]) compared to the placebo arm (24.5%; 95% CI [21.0%; 28.4%]), with a difference in deterioration rate of 2.47 (95% CI: [-1.99%; 6.93%]; p=0.272198).

At baseline, the EQ-5D-3L index score and visual analog scale (VAS) scores were similar between the treatment arms. Small changes in mean values from baseline for both scores were observed in both treatment arms, but there were no clinically meaningful differences (MID = 0.1 for Index Score and 7 for VAS) between the treatment arms at any of the time points.

The index score and VAS score results slightly favoured darolutamide (higher scores represent better HRQoL) but were not statistically significant and were not clinically meaningful, as they did not meet the MID thresholds.

Completion rates of the BPI-SF were comparable between the treatment arms. At baseline (visit 1, day 1), BPI-SF pain severity and pain interference scores were similar between the treatment arms. Changes in mean values from baseline for the pain severity and pain interference scores were observed in both treatment arms, but there were no clinically meaningful differences (MID = 2 points) between the treatment arms at any of the time points.

The pain interference score and pain severity score results favoured darolutamide (lower scores represent less pain) and were statistically significant but were not clinically meaningful, as the difference in least squares (LS) mean between the treatment arms did not meet the MID threshold (MID = 2 points).

Ancillary analyses

Additional MFS analysis

Table 27: MFS analysis with baseline metastasis censored in study 17712 (ARAMIS) (FAS)

	Darolutamide N = 955	Placebo N = 554
Number (%) of patients with event	171 (17.9%)	177 (31.9%)
Number (%) of patients censored	784 (82.1%)	377 (68.1%)
MFS (months)		
Median [95% CI]	40.51 [35.78; A]	22.08 [18.33; 25.76]
Range (including censored values)	(0.03** - 44.28**)	(0.03** - 36.89)
Range (without censored values)	(0.85 - 40.51)	(1.08 - 36.89)
4-month event-free rate [95% CI]	0.967 [0.955; 0.978]	0.882 [0.852; 0.911]
8-month event-free rate [95% CI]	0.928 [0.910; 0.946]	0.774 [0.734; 0.815]
12-month event-free rate [95% CI]	0.871 [0.847; 0.895]	0.683 [0.635; 0.730]
24-month event-free rate [95% CI]	0.737 [0.696; 0.777]	0.447 [0.378; 0.515]
36-month event-free rate [95% CI]	0.573 [0.492; 0.654]	0.288 [0.172; 0.403]
48-month event-free rate [95% CI]	A [A; A]	0.000 [A; A]
Hazard ratio: (darolutamide/placebo) [95% CI] [b]	0.356 [0.287; 0.441]	
Two sided p-value from log-rank test	<0.000001	

A = Value cannot be estimated; CI = Confidence interval; FAS = Full analysis set; MFS = Metastasis-free survival; N = Total number of patients (100%); PSADT = Prostate-specific antigen doubling time.

** Censored observation.

a: Patients with baseline metastasis were censored at the randomization date.

b: A hazard ratio <1 indicates superiority of darolutamide over placebo. Hazard ratio and 95% CI was based on Cox Regression Model, stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy.

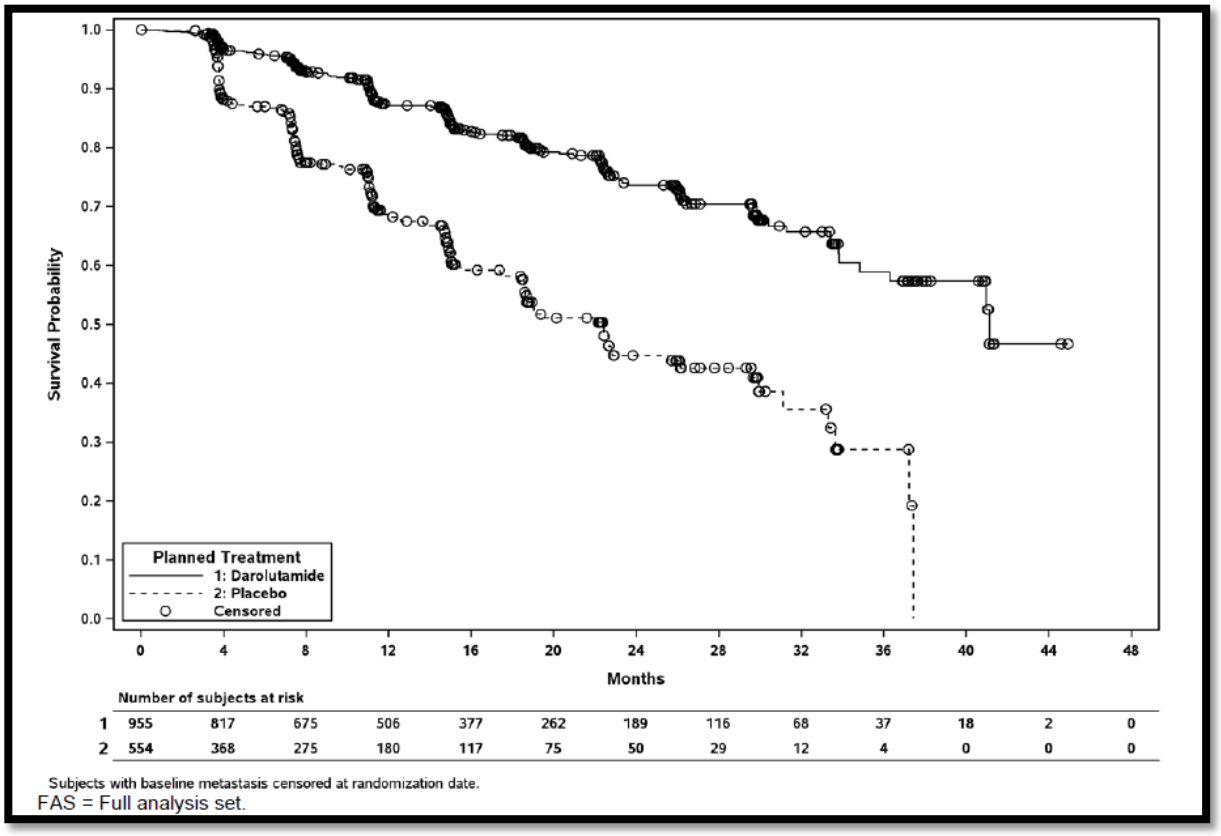


Figure 10: Kaplan-Meier curves of MFS with baseline metastasis censored in study 17712 (ARAMIS) (FAS)

MFS sensitivity analysis

Table 28: Sensitivity analyses of MFS with baseline metastasis non-censored in study 17712 (ARAMIS) (FAS)

Sensitivity analysis		Hazard ratio: Darolutamide/Placebo [95% CI] [a]	Two-sided p-value from log-rank test
Analysis 1	Censoring of patients who died before documented metastasis	0.374 [0.304; 0.459]	<0.000001
Analysis 2	Considering all prohibited new anti-cancer treatment that started prior to documented metastasis as event	0.346 [0.293; 0.409]	<0.000001
Analysis 3 [b]	Using stratification data from the CRF	0.407 [0.336; 0.493]	<0.000001
Analysis 4 [b]	Without including stratification factors in the model	0.417 [0.345; 0.504]	<0.000001
Analysis 5	Using MFS data based on investigator assessment	0.399 [0.337; 0.473]	<0.000001
Analysis 6	Considering all deaths independent of the time of occurrence as MFS events	0.411 [0.341; 0.495]	<0.000001
Analysis 7	Using the event at the date of the first post-baseline scan with metastasis instead of the event at randomization, for patients with baseline metastasis. If no metastasis was documented in post-baseline scans, the patient was censored at the last available scan date. In case the patient did not have any post-baseline scans, the event would remain at baseline and the patient was censored at randomization.	0.391 [0.323; 0.474]	<0.000001
Analysis 8 (post-hoc) [c]	Excluding patients with the primary reason for permanent discontinuation of study treatment of "judgment of investigator" or "personal reason", and without MFS events	0.375 [0.310; 0.453]	<0.000001

CI = confidence interval; CRF = case report form; FAS = full analysis set; MFS = metastasis-free survival

a: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and its 95% CI were based on Cox Regression Model.

b: Note: Descriptive statistics results and Kaplan-Meier curves for sensitivity analysis 3 (using stratification data from the CRF) and sensitivity analysis 4 (without including stratification factors in the model) were exactly the same as in the main analysis.

c: Post-hoc sensitivity analysis 8 excluded patients without an MFS event who permanently discontinued treatment with the primary reason being "judgment of the investigator" (2.4% in the darolutamide arm, 9.2% in the placebo arm) or "personal reason" (5.5% in the darolutamide arm, 10.8% in the placebo arm;

A=value cannot be estimated. The HR and CI were obtained from univariate analysis using unstratified Cox regression. Medians were computed using KM estimates.

MFS subgroup analyses

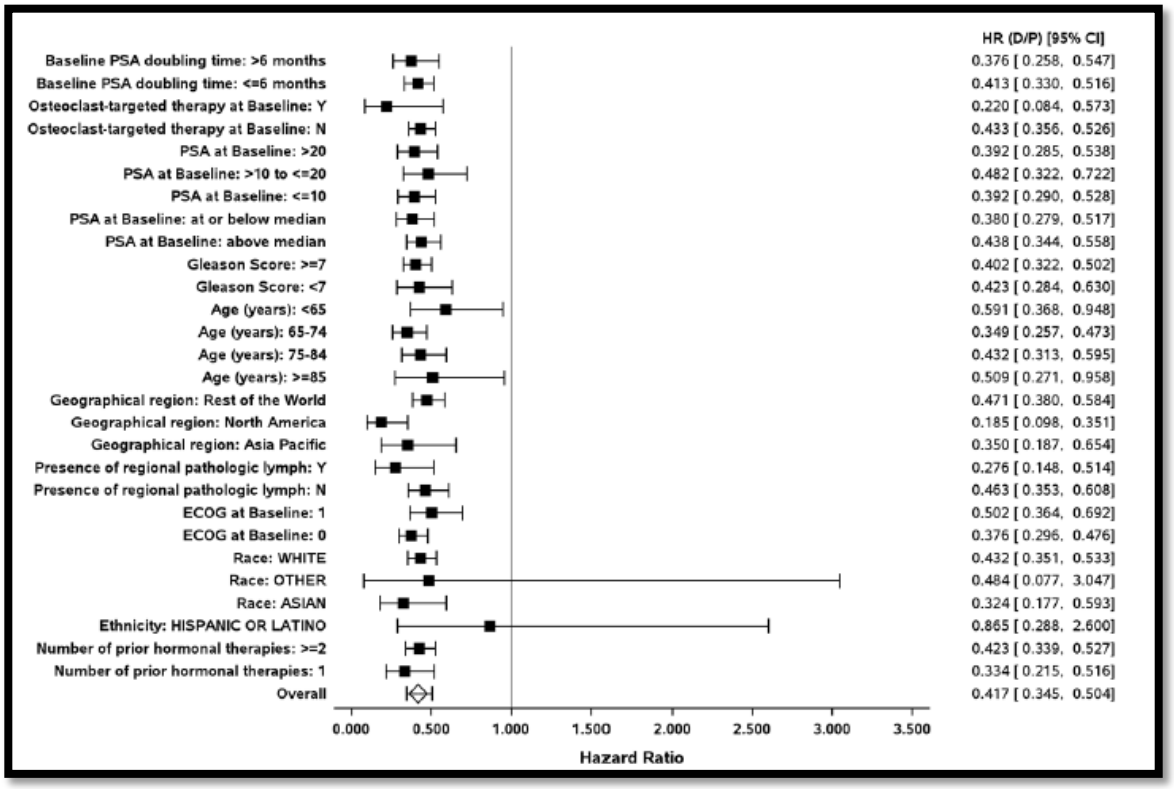


Figure 11: Forest plot of subgroup analyses of MFS with baseline metastasis non-censored (FAS)

Overall survival subgroup analysis

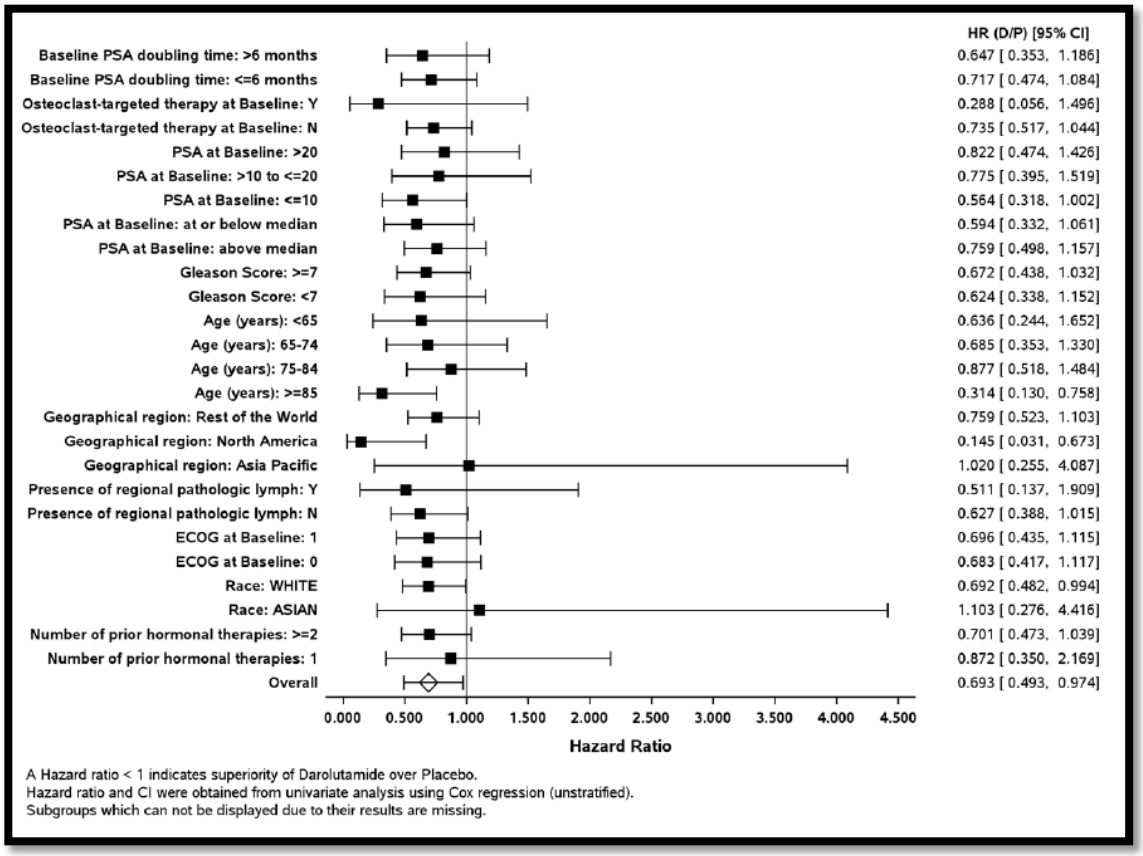


Figure 12: Forest plot of OS subgroup analyses (FAS)

Concomitant bisphosphonate or denosumab therapies

As per protocol, patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis could continue treatment at the same dose and schedule.

38/954 (3.8%) patients in the darolutamide arm and 28/554 (5.1%) in the placebo arm were receiving either a bisphosphonate or denosumab at study entry.

Among patients without osteoclast-target therapy at baseline, 13 (1.4%) and 17 (3.1%) subjects in darolutamide and placebo arms, respectively, started bisphosphonates or denosumab therapies during the study. In the darolutamide group 4/13 patients started bisphosphonates or denosumab for metastasis and 10/17 in the placebo arm.

Summary of main study

The following table summarises 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 29: Summary of efficacy for trial ARAMIS 17712

Title: Aramis is a multinational, randomized, double-blind, placebo-controlled, Phase III efficacy and Safety Study of darolutamide (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer			
Study identifier	Study no.: 17712 EudraCT no.: 2013-003820-36 NCT no.: NCT02200614		
Design	This study is a randomized, double-blind, placebo-controlled, multinational clinical trial.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		47 months not applicable not applicable
Hypothesis	Superiority of darolutamide over placebo		
Treatments groups	Darolutamide arm		954 patients received darolutamide 600 mg (2 tablets of 300 mg) b.i.d. with food, equal to a daily dose of 1200 mg. Concurrently with ADT (At the time of cut-off date of 3 September 2018; 615 patients were on study treatment)
	Placebo arm		554 patients randomized received placebo. Concurrently with ADT (At the time of cut-off date of 3 September 2018; 200 patients were on study treatment)
Endpoints and definitions	Metastasis-Free Survival	MFS	The primary efficacy variable MFS was defined as time from randomization to confirmed evidence of metastasis or death from any cause, whichever occurred first. The analysis included all randomized patients. Deaths before documented metastasis and not later than 32 (+1) weeks after the last evaluable scan were included in this analysis. The primary objective of this study was to demonstrate superiority of darolutamide over placebo in metastasis-free survival (MFS) in patients with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC).

	Overall Survival	OS	OS was defined as time from randomization to death due to any cause. OS of patients not known to have died were censored at their last date of being known to be alive or at the database cut-off date, whichever came first.
	Time to pain progression	*N/A*	Time to pain progression was defined as time from randomization to pain progression, where progression was defined as an increase of 2 or more points from baseline in question 3 of the BPI-SF questionnaire related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores, or initiation of short- or long-acting opioids for cancer pain, whichever came first. Initiation or change in the use of other non-opioid analgesics was not used in the analysis of pain progression.
	Time to cytotoxic chemotherapy	*N/A*	The time to initiation of first cytotoxic chemotherapy was defined as time from randomization to the start of the first cytotoxic chemotherapy cycle.
	Time to first symptomatic skeletal event	SSE	The time to the first SSE was defined as the time from randomization to the occurrence of the first SSE. SSE was defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumour-related orthopaedic surgical intervention.
Database lock	03 SEP 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	A total of 1509 patients on androgen deprivation therapy were randomly assigned in 2:1 ratio to receive study treatment, with 955 patients in the darolutamide arm and 554 patients in the placebo arm. Of the randomized patients, 99.9% of the patients in the darolutamide arm and 100% of the patients in the placebo arm received at least one dose of study drug. One patient was randomized to the darolutamide arm but never received treatment.		
Descriptive statistics and estimate variability	Treatment group	Darolutamide arm	Placebo arm
	Number of subject	955	554

	Metastasis-Free Survival Median [95% CI] Number (%) of patients with event	40.37 [34.33; A] months 221 (23.1%)	18.43 [15.51; 22.34] months 216 (39.0%)
	HR [95% CI]	0.413 [0.341; 0.500]	
	p	<0.000001	
	Overall Survival Median [95% CI] Number (%) of patients with event	A [44.45; A] months 78 (8.2%)	A [A; A] months 58 (10.5%)
	HR [95% CI]	0.706 [0.501; 0.994]	
	p	0.045210	
	Time to pain progression Median [95% CI] Number (%) of patients with event	40.31 [33.21; 41.20] months 251 (26.3%)	25.36 [19.09; 29.63] months 178 (32.1%)
	HR [95% CI]	0.647 [0.533; 0.785]	
	p	0.000008	
	Time to cytotoxic chemotherapy Median [95% CI] Number (%) of patients with event	A [A; A] months 73 (7.6%)	38.21 [35.55; 41.89] months 79 (14.3%)
	HR [95% CI]	0.433 [0.314; 0.595]	
	p	<0.000001	

	Time to first symptomatic skeletal event Median [95% CI] Number (%) of patients with event	 A [A; A] months 16/955 (1.7%)	 A [A; A] months 18/554 (3.2%)
	HR [95% CI]	0.428 [0.218; 0.842]	
	p	0.011262	

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

Not applicable.

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	589	593	130
Non-Controlled Trials	0	0	0

Supportive study(ies)

Supportive studies were Phase 1 and 2 studies in the metastatic prostate cancer setting: ARADES 17829, ARADES EXT 18035 and ARAFOR 17830 (see clinical pharmacology section).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The proposed recommended dose of darolutamide for the treatment of nmCRPC is 600 mg (2 x 300 mg tablet) b.i.d., equal to a total daily dose of 1200 mg. The tablets should be taken whole with food. If a dose is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose. The patient should not take two doses together to make up for a missed dose. The recommended dose was determined based on clinical results from studies in the darolutamide clinical development program, especially study 17829 (ARADES) and study 17830 (ARAFOR) which were conducted in mCRPC patients. This was further supported by the exposure-PSA analysis in mCRPC and nmCRPC patients (study 19792) and non-clinical data. The dose is considered adequately justified.

The pivotal study 17712 (ARAMIS) was designed with two main components: a double blinded part and an open label part which was introduced during the 3rd (and last) protocol amendment prior to the primary analysis to allow patients in the placebo arm to cross over to active darolutamide treatment. This type of cross over can confound the overall survival results which will need to be considered when final results are provided.

The comparator in this study is a placebo which is considered acceptable in this disease setting considering apalutamide and enzalutamide were not yet authorised at the time the study was started. Darolutamide is intended for patients who are only considered high risk for developing metastasis. This is appropriate given the impact metastasis, in particular symptomatic metastasis will have on a patient's long-term survival and quality of life. High risk nmCRPC was defined as a short PSA doubling time (PSADT) of ≤ 10 months and PSA ≥ 2 ng/mL at baseline screening which is acceptable.

The primary endpoint was MFS which is considered an acceptable endpoint in this particular disease setting as patients have a prolonged disease course. CHMP Scientific advice on the clinical development programme and the pivotal study design was obtained in 2013 specifically on the definition of nmCRPC who are at high risk of developing metastasis, the use of MFS as an endpoint, the statistical plan and dose recommendation. The applicant was advised that the events (i.e. metastases) should include both bone and soft tissue metastases and that radiographic progression should be based on RECIST v1.1 criteria.

There were four secondary endpoints which captured important clinical settings in the management of patients with this disease: Overall survival (OS), Time to pain progression, Time to initiation of first cytotoxic chemotherapy for prostate cancer and Time to first symptomatic skeletal event (SSE). PFS and PSA-related endpoints were selected as tertiary and exploratory endpoints. The applicant has provided an adequate justification for including PFS as an exploratory endpoint because in the context of nmCRPC, assessing the occurrence of distant metastases assessed by an MFS endpoint is more relevant as they are the main contributors to illness and death.

The study established a steering committee and an independent data and safety monitoring board. The overall design of the trial in terms of blinding, randomisation 2:1, stratification, inclusion and exclusion criteria is acceptable.

Efficacy data and additional analyses

There were 2696 patients enrolled in the study of which 44.0% were discontinued from screening. A total of 1509 patients were randomly assigned in a 2:1 ratio to one of the following treatment arms: darolutamide (955 patients) or placebo (554 patients). Of the randomized patients, 99.9% of the patients in the darolutamide arm and 100% of the patients in the placebo arm received at least one dose of study drug. One patient was randomized to the darolutamide arm but never received treatment.

The study protocol was amended 3 times prior to the primary analysis. Protocol amendment 2 dated July 2016 clarified the entry criteria further in terms of CRPC definition and PSADT and is not considered to have an impact on the overall study results.

The number of protocol deviations was high. It was clarified that any misunderstanding of study procedures by the site team or a patient as well as missing or accidental use of wrong forms, samples or procedures outside of the allowed time window were reported as protocol deviations and represent the high number of deviations. There was 1 major protocol deviation which occurred in the darolutamide arm whereby one patient was randomised and never received treatment. The deviations classified as important were evenly distributed amongst the two arms.

The median age in both treatment arms was 74.0 years, with most patients being in the age groups of 65-74 years old and 75-84 years old. In the total study population, patients were predominantly white (79.1%), with 12.8% of patients identifying as Asian, 3.4% as black or African American, and 3.1% as Hispanic or Latino.

The median PSA values at baseline were similar between the treatment arms, 9.030 ng/mL and 9.670 ng/mL in the darolutamide and placebo arm. The median time since initial diagnosis to the start of study treatment was 86.15 months in the darolutamide arm and 84.23 months in the placebo arm. The median time from first prior ADT treatment, including GnRH agonist/antagonists, orchiectomy, antiandrogens, to start of study treatment was similar in both treatment arms.

The baseline cancer characteristics show that there was a baseline presence of regional pathological lymph nodes by central imaging review in both treatment groups. 163 (17.1%) in the darolutamide arm and 158 (28.5%) in the placebo arm.

A total of 89 patients were identified by the second review pool to have metastatic disease at baseline retrospectively (*post hoc* analysis of the baseline images). These patients were previously considered eligible by radiology pool 1. The primary MFS analysis included the 89 patients with baseline metastases, counting them as events at randomization.

Prior to being diagnosed as castrate resistant, the types of initial radical treatment received were balanced in both arms. However, given that the median age of patients was 74 years in both arms with nearly 50% of patients in the darolutamide arm ≥75 years, the number of patients receiving radiotherapy (18.5 % vs 16.1%) as an option for curative intent seems lower than what is expected in clinical practice. In both arms, the majority of patients received chemical castration with approximately a quarter of patients undergoing surgery. While active surveillance is an option for men with low risk disease and watchful waiting with delayed hormone therapy can be an option for men unsuitable for radical treatment, in general, primary ADT is not recommended as standard initial treatment of non-metastatic disease. It was clarified that 58.8% of the patients received upfront definitive local therapy based on the information in the CRF.

38/954 (3.8%) patients in the darolutamide arm and 28/554 (5.1%) in the placebo arm were receiving either a bisphosphonate or denosumab at study entry. Among patients without osteoclast-target therapy at baseline, the reported use of osteoclast targeted therapy was 2% in patients in ARAMIS study.

The imbalance observed between the two arms for patients who discontinued without documented metastases as well as without an MFS event (76/955 (7.9%) in the darolutamide arm and 111/554 (20%) in the placebo arm) was principally related to the higher number of patients in the placebo arm who discontinued the study treatment due to the investigator judgement and personal reasons.

According to the ARAMIS clinical study protocol, a patient could continue to receive treatment until metastasis was confirmed by the central review. It was noted that 356 patients (168 in the darolutamide arm and 188 in the placebo arm) have continued to receive treatment beyond metastasis which is a violation of the treatment duration defined in the protocol. These patients were identified centrally during an ongoing central review process called "rolling reads". The interval period between the centralised confirmation of metastasis (CoM) and last exposure to study drug varied amongst participants with no discernible trend from 1 day to 337 days. The applicant has provided a justification for the delay whereby the CoM process could take time due to scan related queries prior to radiological confirmation and scheduling an appointment to inform the patient of their disease progression.

Results from the pivotal study demonstrated a significant treatment effect for MFS with a hazard ratio of 0.413 (95% CI: [0.341; 0.500]; p<0.000001) representing a 58.7% reduction in the risk of metastases or

death in the darolutamide arm compared with the placebo arm. The median MFS was 40.37 months in the darolutamide arm compared to 18.43 months in the placebo arm, which is a clinically meaningful difference of 21.94 months in favour of darolutamide. The event-free rates at 4, 8, 12, 24, and 36 months demonstrate that the benefit of darolutamide treatment with regard to MFS was maintained over time. Importantly a statistically significant MFS result is maintained when baseline metastasis is censored. All sensitivity analyses were consistent with the results of the primary analysis of MFS and supported superiority of darolutamide over placebo.

Moreover, while all participants were classified as high risk, the treatment benefit presented for darolutamide in the subgroup analysis did not depend on prostate cancer specific prognostic features for example baseline PSA value, PSADT or Gleason score at diagnosis. There was also a treatment benefit with darolutamide across all ages, if there were regional pathological LNs present at baseline and if patients received ≥2 lines of hormonal therapies prior to starting darolutamide.

For race/ethnicity, a higher incidence (60% more often) and mortality rates of prostate cancer have been reported in African American male population compared to Caucasian American males. Due to low patient numbers and event counts, the CIs were wide for the subgroups 'Ethnicity: Hispanic or Latino' (N = 47, N with event = 14) and 'Race: Other' (N = 15, N with event = 5), thus the results for these subgroups have to be interpreted with caution.

Overall, secondary endpoints (OS, time to pain progression, time to cytotoxic chemotherapy, and time to first symptomatic skeletal event) showed consistency with primary efficacy outcomes. At the time of primary analysis for MFS, 136 OS events had occurred out of the planned 240 events for the final analysis. Despite the low number of events presented, treatment with darolutamide does not negatively impact OS with a HR of 0.706. The median was not reached in either treatment arm. The available immature OS data have not shown a detrimental effect which is reassuring. To further investigate the efficacy of darolutamide in this setting, the applicant will provide the final clinical study report including the results of the final analysis for OS by 30 June 2020 (PAES, Annex II).

Time to pain progression translated as a difference of 14.95 months in favour of the darolutamide arm. In general patients are asymptomatic at this point from their disease and therefore should be essentially pain free at baseline from their prostate cancer specifically an opiate naive.

Time to initiation of first cytotoxic chemotherapy is considered particularly noteworthy given the fact that PFS2 has not been formally analysed in this pivotal study. In terms of events, only 73/955 (7.6%) in the darolutamide arm and 79/554 (14.3%) in the placebo arm had occurred at the time of primary analysis. Time to initiation of subsequent antineoplastic therapy excluding cytotoxic chemotherapy was also assessed as an additional endpoint and a post-hoc analysis of subsequent antineoplastic therapy and/or cytotoxic chemotherapy in patients who discontinued study treatment was performed. Delaying the initiation of subsequent therapies for metastasis and opiate analgesia to control cancer related pain are relevant for the management of nmCRPC.

Time to first symptomatic skeletal event captures 4 clinically important presentations which are relevant to efficacy but also the management of patients with prostate cancer; palliative radiotherapy for bone metastasis, spinal cord compression, orthopaedic surgical intervention, new pathological bone fracture. Because of the low number of events at the time of analysis, a statistically significant difference has not been demonstrated however there is a positive trend in favour of darolutamide.

There were additional objectives to the pivotal study which determined the benefit of darolutamide for progression free survival, time to first prostate cancer related invasive procedure and time to initiation of first

subsequent antineoplastic therapy along with objectives to determine the effect of darolutamide on PSA progression and response, ECOG performance status deterioration and health related QoL. There was a delay in PSA progression, PFS and time to initiation of subsequent therapies in the patients who received darolutamide. The median PFS in the darolutamide arm was 36.83 months versus 14.82 months in the placebo arm with a HR of 0.380. Evaluating the QoL is crucial because of patient's good performance status prior to receiving treatment. QoL was not impaired and the delay of time to deterioration in post hoc analysis could be translated as an improvement in patients QoL compared to placebo.

Overall, the data presented for the secondary and additional exploratory objectives while encouraging, are too immature to draw any firm conclusions.

2.5.4. Conclusions on the clinical efficacy

Overall the pivotal study ARAMIS met its primary endpoint which demonstrated a statistically significant benefit in terms of MFS for patients with non-metastatic CRPC. The use of darolutamide demonstrates an important delay in the onset of distant metastases, which appears to be supported by secondary endpoints for the time being. The final clinical study report, including update on OS and other secondary endpoints, is warranted to further investigate the benefit of this treatment.

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

PAES: In order to further investigate the efficacy of darolutamide in adult men with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease, the MAH should submit the final study report, including updated OS results, from study ARAMIS 17712. Due date: 30 June 2020

2.6. Clinical safety

Patient exposure

Four separate data sources contribute to the analyses of clinical safety for darolutamide (see also Table 17):

1. Pivotal study 17712 (nmCRPC), darolutamide arm N=954 (primary analysis of safety)
2. mCRPC pool, N=173: pooled analysis of four uncontrolled Phase 1 and Phase 2 studies in metastatic castration-resistant prostate cancer (mCRPC) patients (Study 17829 (ARADES), Study 18035 (ARADES-EXT), Study 17830 (ARAFOR) and Study 17719).
3. Non-cancer subjects pool: single dose N=56, multiple dose N=45
4. Ongoing blinded study 17777 (mHSPC), darolutamide arm N ~ estimated 650 patients

In the pivotal study 17712 ARAMIS treatment exposure was longer in the darolutamide arm months (14.8 months [range: <0.1 to 44.3 months]) versus the placebo arm (11.0 months [range: 0.1 to 40.5 months]). More than half of patients in the darolutamide arm (51.7% darolutamide vs 36.8% placebo) received treatment >12 months to </= 30 months. The percentage receiving treatment beyond 30 months was also higher in the darolutamide arm (9.1%) than in the placebo arm (3.2%). More than 500 patients in the darolutamide arm in study 17712 were treated for >12 months. As of the cut-off date 3 September 2018, 64.4% of patients in darolutamide arm vs 36.1% patients in placebo arm were still receiving treatment. The most common reason

for treatment discontinuation in both arms was confirmed metastasis (11.7% in darolutamide arm vs 23.3% in placebo arm). The numbers who discontinued due to an AE was relatively similar between both arms (8.9% in darolutamide arm vs 8.7% in placebo).

Table 30: Study drug exposure in nmCRPC study 17712 (SAF)

	Darolutamide	Placebo
	N = 954	N = 554
Overall time under treatment (months) [a]		
N	954	554
Mean	16.79	12.30
StD	9.46	8.32
Min	0.0	0.1
Median	14.80	11.04
Max	44.3	40.5
Overall time under treatment (months) - categories, n (%) [a]		
≤1	16 (1.7%)	9 (1.6%)
>1 to ≤6	78 (8.2%)	136 (24.5%)
>6 to ≤12	280 (29.4%)	187 (33.8%)
>12 to ≤18	172 (18.0%)	93 (16.8%)
>18 to ≤24	188 (19.7%)	67 (12.1%)
>24 to ≤30	133 (13.9%)	44 (7.9%)
>30 to ≤36	46 (4.8%)	9 (1.6%)
>36	41 (4.3%)	9 (1.6%)
Actual daily dose (mg/day) [b]		
N	954	554
Mean	1186.61	1192.47
StD	64.64	49.56
Min	550.0	596.8
Median	1200.00	1200.00
Max	1200.0	1200.0

	Darolutamide	Placebo
	N = 954	N = 554
Percent of planned dose [c]		
N	954	554
Mean	98.88	99.37
StD	5.39	4.13
Min	45.8	49.7
Median	100.00	100.00
Max	100.0	100.0
Percent of planned dose - categories, n (%) [c]		
> 30 to 60%	7 (0.7%)	3 (0.5%)
> 60 to 90%	20 (2.1%)	6 (1.1%)
> 90 to 100%	927 (97.2%)	545 (98.4%)

Adverse events

An overview of TEAEs in prostate cancer patients treated with darolutamide or placebo concurrently with ADT is presented in Table 37 until the cut-off dates for the respective CSRs.

Table 31: Overview of TEAEs in prostate cancer patients (SAF)

		nmCRPC study 17712		mCRPC pool
		Darolutamide	Placebo	Darolutamide
Number of patients (%) with		**N = 954**	**N = 554**	**N = 173**
		n (%)	**n (%)**	**n (%)**
Any TEAE [a]		**794 (83.2%)**	**426 (76.9%)**	**162 (93.6%)**
Worst CTCAE grade:	Grade 1	219 (23.0%)	134 (24.2%)	32 (18.5%)
	Grade 2	302 (31.7%)	166 (30.0%)	81 (46.8%)
	Grade 3	215 (22.5%)	99 (17.9%)	37 (21.4%)
	Grade 4	21 (2.2%)	9 (1.6%)	5 (2.9%)
	Grade 5 (death/fatal)	37 (3.9%)[d]	18 (3.2%)	7 (4.0%)[e]
	Grade 1 or 2	521 (54.6%)	300 (54.2%)	113 (65.3%)
	Grade 3 or 4	236 (24.7%)	108 (19.5%)	42 (24.3%)
	Grade 3, 4 or 5	273 (28.6%)	126 (22.7%)	49 (28.3%)
SAE		237 (24.8%)	111 (20.0%)	48 (27.7%)
TEAE leading to dose modification [b]		135 (14.2%)	52 (9.4%)	20 (11.6%)
TEAE leading to permanent discontinuation of study drug		85 (8.9%)	48 (8.7%)	13 (7.5%)
Any drug-related TEAE [a,]		**258 (27.0%)**	**110 (19.9%)**	**61 (35.3%)**
Worst CTCAE grade:	Grade 1	132 (13.8%)	68 (12.3%)	43 (24.9%)
	Grade 2	98 (10.3%)	26 (4.7%)	16 (9.2%)
	Grade 3	24 (2.5%)	14 (2.5%)	2 (1.2%)
	Grade 4	3 (0.3%)	0 (0.0%)	0 (0.0%)
	Grade 5 (death/fatal)	1 (0.1%)	2 (0.4%)	0 (0.0%)
	Grade 1 or 2	230 (24.1%)	94 (17.0%)	59 (34.1%)
	Grade 3 or 4	27 (2.8%)	14 (2.5%)	2 (1.2%)
	Grade 3, 4 or 5	28 (2.9%)	16 (2.9%)	2 (1.2%)
Drug-related SAE		10 (1.0%)	6 (1.1%)	1 (0.6%)
Drug-related TEAE leading to dose modification [b]		49 (5.1%)	14 (2.5%)	3 (1.7%)
Drug-related TEAE leading to permanent discontinuation of study drug		15 (1.6%)	13 (2.3%)	2 (1.2%)
Any death		**79 (8.3%)**	**58 (10.5%)**	**7 (4.0%)**

CTCAE = Common Terminology Criteria for Adverse Events; mCRPC = Metastatic castration-resistant prostate cancer; N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; SAE = Serious adverse event; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event

a: Any TEAE also includes patients with grade not available for all AEs.

b: Modifications include dose interruptions and reductions.

c: Based on investigator's assessment.

d: For some of the patients in the darolutamide arm, the start of grade 5 TEAE was reported within 30 days of the last dose but the death occurred more than 30 days after treatment discontinuation or after the report cut-off date.

e: For 1 patient in study 17829, the start of grade 5 TEAE was reported within 30 days of the last dose, but the death occurred more than 30 days after treatment discontinuation.

CTCAE version 4.03.

nmCRPC study 17712: Module 5.3.5.1, Report PH-39723, Table 14.3.1/1, Table 14.3.2/12 and Listing 16.2.7/1.

mCRPC pool: Module 5.3.5.3, IA mCRPC, Table 3.1/1, Table 3.2/2 and Table 3.2/3

Common adverse events

An overview of the TEAEs reported in ≥2% of patients in either treatment arm in study 17712 is presented by MedDRA PT in Table 38. To adjust for unequal lengths of the study treatment duration between the treatment arms, exposure-adjusted incidence rates (EAIRs) per 100 patient years (PYs) are also summarized.

Table 32: Most common TEAEs and exposure-adjusted TEAEs by MedDRA PT occurring in ≥2% of patients in either arm in nmCRPC study 17712 (SAF)

	Darolutamide N = 954					Placebo N = 554				
MedDRA PT Version 21.0	Total n (%)	EAIR per 100 PY [a]	Worst CTCAE grade Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)	EAIR per 100 PY [a]	Worst CTCAE grade Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Fatigue	115 (12.1)	8.6	4 (0.4)	0	0	48 (8.7)	8.5	5 (0.9)	0	0
Back pain	84 (8.8)	6.3	4 (0.4)	0	0	50 (9.0)	8.8	1 (0.2)	0	0
Arthralgia	77 (8.1)	5.8	3 (0.3)	0	0	51 (9.2)	9.0	2 (0.4)	0	0
Diarrhoea	66 (6.9)	4.9	0	0	1 (0.1)	31 (5.6)	5.5	1 (0.2)	0	0
Hypertension	63 (6.6)	4.7	30 (3.1)	0	0	29 (5.2)	5.1	12 (2.2)	0	0
Constipation	60 (6.3)	4.5	0	0	0	34 (6.1)	6.0	0	0	0
Pain in extremity	55 (5.8)	4.1	0	0	0	18 (3.2)	3.2	1 (0.2)	0	0
Anaemia	53 (5.6)	4.0	8 (0.8)	0	0	25 (4.5)	4.4	2 (0.4)	0	0
Hot flush	50 (5.2)	3.7	0	0	0	23 (4.2)	4.1	0	0	0
Nausea	48 (5.0)	3.6	2 (0.2)	0	0	32 (5.8)	5.6	0	0	0
Urinary tract infection	47 (4.9)	3.5	6 (0.6)	0	0	28 (5.1)	4.9	3 (0.5)	0	0
Haematuria	41 (4.3)	3.1	10 (1.0)	0	0	27 (4.9)	4.8	7 (1.3)	0	0
Oedema peripheral	39 (4.1)	2.9	0	0	0	17 (3.1)	3.0	0	0	0
Pollakiuria	38 (4.0)	2.8	1 (0.1)	0	0	16 (2.9)	2.8	1 (0.2)	0	0
Headache	37 (3.9)	2.8	0	0	0	14 (2.5)	2.5	1 (0.2)	0	0
Musculoskeletal pain	37 (3.9)	2.8	1 (0.1)	0	0	11 (2.0)	1.9	1 (0.2)	0	0
Asthenia	36 (3.8)	2.7	2 (0.2)	0	0	19 (3.4)	3.3	2 (0.4)	0	0
Fall	36 (3.8)	2.7	8 (0.8)	0	0	23 (4.2)	4.1	4 (0.7)	0	0
Nasopharyngitis	36 (3.8)	2.7	0	0	0	21 (3.8)	3.7	0	0	0
Dizziness	35 (3.7)	2.6	2 (0.2)	0	0	14 (2.5)	2.5	1 (0.2)	0	0
Weight decreased	34 (3.6)	2.5	0	0	0	12 (2.2)	2.1	0	0	0
Urinary retention	33 (3.5)	2.5	15 (1.6)	0	0	36 (6.5)	6.3	11 (2.0)	0	0
Cough	29 (3.0)	2.2	1 (0.1)	0	0	11 (2.0)	1.9	0	0	0

Decreased appetite	28 (2.9)	2.1	2 (0.2)	0	0	16 (2.9)	2.8	1 (0.2)	0	0
Influenza	27 (2.8)	2.0	0	1 (0.1)	1 (0.1)	9 (1.6)	1.6	0	0	0
Insomnia	26 (2.7)	1.9	0	0	0	10 (1.8)	1.8	1 (0.2)	0	0
Upper respiratory tract infection	25 (2.6)	1.9	0	0	0	9 (1.6)	1.6	0	0	0
Abdominal pain	24 (2.5)	1.8	0	1 (0.1)	0	12 (2.2)	2.1	1 (0.2)	0	0
Dyspnoea	24 (2.5)	1.8	2 (0.2)	0	1 (0.1)	15 (2.7)	2.6	3 (0.5)	0	0
Atrial fibrillation	22 (2.3)	1.6	5 (0.5)	1 (0.1)	0	8 (1.4)	1.4	1 (0.2)	1 (0.2)	0
Blood creatinine increased	22 (2.3)	1.6	1 (0.1)	0	0	14 (2.5)	2.5	0	2 (0.4)	0
Dysuria	21 (2.2)	1.6	1 (0.1)	0	0	26 (4.7)	4.6	5 (0.9)	0	0
Gynaecomastia	19 (2.0)	1.4	0	0	0	6 (1.1)	1.1	0	0	0
Pneumonia	19 (2.0)	1.4	8 (0.8)	1 (0.1)	1 (0.1)	11 (2.0)	1.9	3 (0.5)	1 (0.2)	0
Pyrexia	19 (2.0)	1.4	1 (0.1)	0	0	5 (0.9)	0.9	0	0	0
Pruritus	16 (1.7)	1.2	0	0	0	11 (2.0)	1.9	0	0	0
Urinary incontinence	14 (1.5)	1.0	0	0	0	12 (2.2)	2.1	0	0	0
Abdominal pain upper	12 (1.3)	0.9	1 (0.1)	0	0	13 (2.3)	2.3	1 (0.2)	0	0
Pelvic pain	12 (1.3)	0.9	0	0	0	12 (2.2)	2.1	0	0	0
Hydronephrosis	10 (1.0)	0.7	7 (0.7)	0	0	13 (2.3)	2.3	3 (0.5)	0	0

CTCAE = Common Terminology Criteria for Adverse Events; EAIR = Exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; PT = Preferred term; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event

a: EAIR of TEAEs, defined as the number of patients with a given TEAE divided by the total treatment duration of all patients in years. The rate is expressed in 100 patient years.

Note: A patient may have more than one entry.

CTCAE version 4.03.

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.1/3 and Table 14.3.1/7

Table 39 shows the incidence of TEAEs that were reported in ≥2% of patients in the mCRPC pool by MedDRA PT.

Table 33: Most common TEAEs by MedDRA PT occurring in ≥2% of patients in mCRPC pool (SAF)

	Darolutamide N = 173 n (%)			
		Worst CTCAE grade		
MedDRA PT Version 21.0	Total	Grade 3	Grade 4	Grade 5
Fatigue	44 (25.4%)	3 (1.7%)	0	0
Back pain	36 (20.8%)	4 (2.3%)	0	0
Nausea	30 (17.3%)	3 (1.7%)	0	0
Arthralgia	27 (15.6%)	2 (1.2%)	0	0
Decreased appetite	26 (15.0%)	0	0	0
Pain	24 (13.9%)	3 (1.7%)	0	0
Constipation	23 (13.3%)	0	0	0
Diarrhoea	21 (12.1%)	0	0	0
Musculoskeletal pain	17 (9.8%)	0	0	0
Vomiting	17 (9.8%)	1 (0.6%)	0	0
Anaemia	16 (9.2%)	6 (3.5%)	0	0
Insomnia	15 (8.7%)	1 (0.6%)	0	0
Headache	14 (8.1%)	1 (0.6%)	0	0
Oedema peripheral	13 (7.5%)	0	0	0
Muscular weakness	12 (6.9%)	1 (0.6%)	0	0
Pain in extremity	12 (6.9%)	0	0	0
Bone pain	11 (6.4%)	1 (0.6%)	0	0
Hot flush	11 (6.4%)	0	0	0
Hypertension	11 (6.4%)	2 (1.2%)	0	0
Weight decreased	11 (6.4%)	0	0	0
Dyspnoea	10 (5.8%)	0	1 (0.6%)	0
Fall	10 (5.8%)	1 (0.6%)	0	0
Haematuria	10 (5.8%)	0	1 (0.6%)	0
Cough	9 (5.2%)	0	0	0
Nasopharyngitis	9 (5.2%)	0	0	0
Abdominal pain	8 (4.6%)	1 (0.6%)	0	0
Asthenia	8 (4.6%)	0	0	0
Chest pain	8 (4.6%)	0	0	0
Dizziness	8 (4.6%)	0	0	0
Gynaecomastia	8 (4.6%)	0	0	0
Pyrexia	8 (4.6%)	0	0	0
Rash	8 (4.6%)	0	0	0
Urinary tract infection	8 (4.6%)	0	0	0
Dyspepsia	7 (4.0%)	0	0	0
Influenza	7 (4.0%)	0	0	0
Blood alkaline phosphatase increased	6 (3.5%)	3 (1.7%)	0	0
Contusion	6 (3.5%)	0	0	0
Dysuria	6 (3.5%)	0	0	0
Flatulence	6 (3.5%)	0	0	0
Hydronephrosis	6 (3.5%)	0	0	0
Muscle spasms	6 (3.5%)	0	0	0
Urinary incontinence	6 (3.5%)	0	0	0
Abdominal distension	5 (2.9%)	0	0	0
Atrial fibrillation	5 (2.9%)	1 (0.6%)	0	0

Infection	5 (2.9%)	2 (1.2%)	0	0
Laceration	5 (2.9%)	1 (0.6%)	0	0
Myalgia	5 (2.9%)	0	0	0
Peripheral swelling	5 (2.9%)	0	0	0
Prostate cancer	5 (2.9%)	1 (0.6%)	0	3 (1.7%)
Urinary retention	5 (2.9%)	2 (1.2%)	0	0
Acute kidney injury	4 (2.3%)	3 (1.7%)	0	0
Blood lactate dehydrogenase increased	4 (2.3%)	0	0	0
Blood urine present	4 (2.3%)	0	0	0
Cancer pain	4 (2.3%)	0	0	0
Dry mouth	4 (2.3%)	0	0	0
Dry skin	4 (2.3%)	0	0	0
Epistaxis	4 (2.3%)	0	0	0
Erythema	4 (2.3%)	0	0	0
Gastroenteritis	4 (2.3%)	0	0	0
General physical health deterioration	4 (2.3%)	1 (0.6%)	0	3 (1.7%)
Hypokalaemia	4 (2.3%)	0	0	0
Lymphoedema	4 (2.3%)	1 (0.6%)	1 (0.6%)	0
Malaise	4 (2.3%)	0	0	0
Neck pain	4 (2.3%)	0	0	0
Paraesthesia	4 (2.3%)	0	0	0
Pelvic pain	4 (2.3%)	0	0	0
Pollakiuria	4 (2.3%)	0	0	0
Pyelonephritis	4 (2.3%)	2 (1.2%)	0	0
Rectal haemorrhage	4 (2.3%)	0	0	0
Rib fracture	4 (2.3%)	0	0	0

mCRPC = Metastatic castration-resistant prostate cancer; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients (100%); n = Number of patients with event; PT = Preferred term; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event

Most common drug-related TEAEs

Overall, TEAEs that were assessed as drug-related by the investigator occurred in 27.0% of patients in the darolutamide arm and in 19.9% of patients in the placebo arm in study 17712. Drug-related events that were reported in ≥2% of patients in the darolutamide or placebo treatment arms, respectively, included fatigue (7.1% vs. 4.3%), hot flush (3.8% vs. 2.7%) and nausea (2.5% vs. 3.1%).

Adverse Events of Grade 3 or 4

Overall, events with grade 3 as the worst grade were reported in 22.5% of patients in darolutamide arm and 17.9% of patients in placebo arm. Of the Grade 3 TEAEs, hypertension was the most common event in both treatment arms with an incidence of 3.1% and 2.2% in the darolutamide and placebo arms, respectively. Grade 3 urinary retention and haematuria were more commonly reported in the placebo arm than darolutamide arm.

For Grade 4 TEAEs, overall incidence was low, 2.2% of patients in darolutamide arm and 1.6% of patients in placebo arm respectively. Of TEAEs with Grade 4 as worst grade, acute myocardial infarction, hyperglycaemia, ischemic stroke and respiratory failure occurred in 0.2% of patients each (n=2), with no corresponding events reported in the placebo arm.

Grade 3 was the worst grade of drug-related TEAEs in 2.5% of patients in both treatment arms. The incidences of drug-related hypertension (0.4% vs. 0.5%) and fatigue (0.2% vs. 0.2%) with worst grade of 3 were similar between darolutamide and placebo arms, respectively. In the darolutamide arm, drug-related events with worst grade of 3 of AST increased and neutrophil count decreased were both reported in 0.3% of patients, and ALT increased, hyponatremia, and neutropenia were reported in 0.2% of patients each in the darolutamide arm. No respective events occurred in the placebo arm.

Grade 4 was the worst grade of drug-related TEAEs in 3 patients (0.3%) in the darolutamide arm and included abnormal hepatic function, ischemic stroke, and pulmonary embolism. No drug-related events with worst grade of 4 were observed in the placebo arm.

Analysis of Special topics

The applicant defined special topics as events/disorders representing potential or known risks associated with ADT or with novel anti-androgens. The overall incidence of TEAEs and exposure adjusted TEAEs for all special topics in study 17712 are presented in **Table 40Error! Reference source not found.**.

Table 34: Incidence of TEAEs and exposure-adjusted TEAEs for special topics in nmCRPC study 17712 (SAF)

	Darolutamide		Placebo		
Grouped TEAE term [a]	N = 954 n (%)	EAIR per 100 PY [b]	N = 554 n (%)	EAIR per 100 PY [b]	Incidence risk ratio for EAIR
Bone fracture	40 (4.19%)	3.0	20 (3.61%)	3.5	0.85
Fall [c]	40 (4.19%)	3.0	26 (4.69%)	4.6	0.65
Fatigue/asthenic conditions	151 (15.83%)	11.3	63 (11.37%)	11.1	1.02
Weight decreased	34 (3.56%)	2.5	12 (2.17%)	2.1	1.21
Seizures	2 (0.21%)	0.1	1 (0.18%)	0.2	0.85
Rash	28 (2.94%)	2.1	5 (0.90%)	0.9	2.38
Cardiac disorders (SOC)	113 (11.8%)	N/A	41 (7.4%)	N/A	N/A
Cardiac arrhythmias	64 (6.71%)	4.7	22 (3.97%)	3.8	1.24
Coronary artery disorders	31 (3.25%)	2.3	14 (2.53%)	2.4	0.94
Heart failures	18 (1.89%)	1.3	5 (0.90%)	0.9	1.53
CNS vascular disorders	16 (1.68%)	1.2	10 (1.81%)	1.7	0.68
Cerebral ischaemia	13 (1.36%)	1.0	8 (1.44%)	1.4	0.69
Cerebral and intracranial haemorrhage	2 (0.21%)	0.1	2 (0.36%)	0.4	0.43
Hypertension	70 (7.34%)	5.2	33 (5.96%)	5.8	0.90
Vasodilatation and flushing	54 (5.66%)	4.0	23 (4.15%)	4.1	1.00
Diabetes mellitus and hyperglycaemia	22 (2.31%)	1.6	12 (2.17%)	2.1	0.78
Mental impairment disorders	16 (1.68%)	1.2	10 (1.81%)	1.7	0.68
Depressed mood disorders	17 (1.78%)	1.3	8 (1.44%)	1.4	0.90
Breast disorders/gynecomastia	22 (2.31%)	1.6	9 (1.62%)	1.6	1.04

CNS = Central nervous system; EAIR = Exposure-adjusted incidence rate; excl = Excluding; incl = Including; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients (100%); n = Number of patients with event; N/A = Not available; nc = Not calculable; nmCRPC = Non-metastatic castration-resistant prostate cancer; PT = Preferred term; PY = Patient year; SAF = Safety analysis set; SAP = Statistical analysis plan; SOC = System organ class; TEAE = Treatment-emergent adverse event

Note: The table contains counts of patients. If a patient experienced more than one episode of an AE, the patient is counted only once within a grouped term.

a: The specific terms used for MedDRA searches and reported PTs for grouped TEAE terms are described separately for each special topic in the subsections below.

b: EAIR of grouped events, defined as the number of patients with events divided by treatment duration in years. The rate is expressed in 100 patient years.

c: After review of the data, the search term for 'Fall' was extended to include also the MedDRA PT 'Accident' by SAP supplement 1.0 (Module 5.3.5.1, Report PH-39723, Section 16.1.9, Section 6.4).

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.1/7s1, Table 14.3.1/8s1, Table 14.3.1/9s1, and Table 14.3.1/10s1

Bone fracture

Treatment emergent events concerning bone fracture were observed with a small difference between the darolutamide and placebo arms (4.19% vs. 3.61%, respectively). When adjusted for the difference in treatment duration between the treatment arms, the rates were 3.0 vs. 3.5 per 100 PY, respectively, with an incidence risk ratio of 0.85 for darolutamide/placebo. Of note, there was also 1 patient in the placebo group (0.2%) who had pathological fracture (not part of the grouped term).

Fractures were reported with worst grade of 1 or 2 in severity in most patients. Fractures with worst grade of 3 were reported in 0.9% of patients in both treatment arms.

The events were considered serious in 0.8% of patients in the darolutamide arm and in 1.1% of patients in the placebo arm. One patient (0.2%) in the placebo arm discontinued study treatment permanently due to a fracture event (grade 3 facial bones fracture). Fracture led to dose interruption in 1 patient in both the darolutamide (0.1%) and placebo arms (0.2%). No dose reductions were reported due to fracture events.

At study entry, the use of osteoclast-targeted therapy was reported only for 3.8% and 5.1% of patients in the darolutamide and placebo arms, respectively.

At study entry a similar proportion of patients received bone sparing agents in darolutamide and placebo arms (123 patients, 12.9% vs. 72 patients, 13.0%, respectively). Drugs included in the bone sparing agents category were selected based on ATC codes and include drugs affecting bone structure and mineralization (such as bisphosphonates and denosumab), vitamin D and analogues, calcium and calcium combinations, fluorides and calcitonins. Altogether 38 of the 123 patients in the darolutamide arm and 28 of the 72 patients in the placebo arm received bisphosphonates or denosumab. The remaining patients received drugs from the other categories (vitamin D and analogues, calcium and calcium combinations, fluorides and calcitonins).

A total of 4.0% and 2.7% of patients in the darolutamide and placebo arms, respectively, had a fracture event during the study but did not receive bone sparing agents while 0.2% and 0.9% of patients had a fracture event and received bone sparing agents. Per protocol, the use of osteoclast-targeted therapy was allowed for the treatment of osteoporosis and was reported for 3.8% and 5.1% of patients at randomization, respectively. Osteoclast targeted therapy was collected in the CRF as a stratification factor and no specific drug names were identified.

No differences were observed between the treatment arms in the cumulative incidence of fractures.

There was a comparable distribution of weight changes in patients with bone fractures in both treatment arms. This result indicates that the risk of fractures does not correlate with a decrease of body weight in patients in either treatment arm. Events of decreased weight were reported in 3.56% of patients in the darolutamide arm and in 2.17% in the placebo arm.

Fall

Treatment-emergent event of ‘fall’ as a single MedDRA PT was reported in 3.8% of patients in the darolutamide arm and 4.2% of patients in the placebo arm.

The events of fall were reported with worst grade of 1 or 2 in severity in most patients and thus were minor with no resultant injuries or symptomatic with non invasive intervention needed. Fall with worst grade of 3 (the highest grade for fall per CTCAE) was reported at a similar level in both darolutamide and placebo arms (0.8% vs. 0.7%, respectively).

SAE of fall was reported in 0.3% of patients in the darolutamide arm and in 0.2% in the placebo arm. No TEAEs leading to permanent discontinuation of study treatment due to fall were reported. The dose was interrupted in 1 patient (0.2%) in the placebo arm as a result of fall. No dose reductions were required.

After review of the data, the MedDRA search term was extended to include also the MedDRA PT 'accident' by the SAP supplement 1.0, since for all cases of 'accident' the reported term was fall. After this modification, fall event as a grouped term was reported in 4.19% and 4.69% of patients in the darolutamide and placebo arms, respectively.

One patient in the placebo arm experienced an accidental fall and syncope (reported terms) on the same day during the study treatment period.

Fatigue/asthenic conditions

Treatment-emergent events of fatigue/asthenic conditions were reported in 15.83% of patients in the darolutamide arm and in 11.37% of patients in the placebo arm.

Fatigue (not including asthenia, lethargy or malaise) occurred in the majority of patients (12.1% of patients treated with darolutamide and 8.7% of patients treated with placebo).

When adjusted for the difference in treatment duration, the incidence of fatigue/asthenic conditions in patients treated with darolutamide was similar to those receiving placebo (11.3 vs. 11.1 per 100 PY, respectively, with an incidence risk ratio of 1.02)

Events of fatigue/asthenic conditions were reported with worst grade of 1 or 2 in severity in most patients. Events with worst grade of 3 were reported in 0.6% of patients in the darolutamide arm and in 1.1% in the placebo arm.

The event was considered serious in 1 patient in the darolutamide arm (grade 3 asthenia). Events of fatigue/asthenic conditions resulted in permanent treatment discontinuation in 0.3% and 0.2% of patients in the darolutamide and placebo arms, respectively. Events led to dose interruption in 0.3% vs. 0.7% of patients, respectively; and to dose reduction in 0.8% vs. 0.5% of patients

The interval-specific incidence of asthenic conditions was comparable between the darolutamide and placebo arms with the highest values observed within the first month of treatment (4.5% in darolutamide and 2.8% in placebo) abating after the first year of exposure. A slightly higher incidence within the first 16 weeks was observed in the darolutamide arm.

The prevalence rate of asthenic conditions reached the highest values in both treatment arms within the first year, abating afterwards faster in placebo arm. The prevalence rate was consistently higher in the darolutamide than in the placebo treatment arm, showing a difference of 1.6 to 2.9 percentage points during the first year of the exposure.

Weight decreased

Treatment-emergent events of weight decreased were reported in 3.56% of patients in the darolutamide arm and in 2.17% of patients in the placebo arm. When adjusted for the difference in treatment duration between the treatment arms, the incidence was similar in patients treated with darolutamide compared to those receiving placebo (2.5 vs. 2.1 per 100 PY, respectively, with an incidence risk ratio of 1.21)

All events were reported with worst grade of 1 (2.3% vs. 1.8%) or grade 2 (1.3% vs. 0.4%) in both darolutamide and placebo arms, respectively.

No SAEs or events leading to permanent discontinuation of study drug were reported in either arm. Dose interruption and dose reduction due to decreased weight was required in 1 patient each (0.2%) in the placebo arm.

No differences were observed between the treatment arms in the changes of mean values over time for body weight.

Seizure

The pre-clinical and clinical data for darolutamide did not indicate any pro-convulsive potential as darolutamide might have low penetration of the blood brain barrier. Therefore, patients with a history of seizure were allowed to enter the study 17712. Overall, 12 patients in the darolutamide arm had a history of seizure (MLG seizures) including 2 patients (0.2%) with seizure and 10 patients (1.0%) with epilepsy. One patient in the placebo arm (0.2%) was reported with post-traumatic epilepsy ongoing at screening.

The incidence of seizure events reported during the study treatment was similar in both treatment arms. The events were reported for 2 patients (0.21%) in the darolutamide arm and for 1 patient (0.18%) in the placebo arm. None of the patients with a medical history of seizure experienced a TEAE of seizure in the darolutamide arm.

Seizures were reported with worst grade of 1 or 2 in both treatment arms. The events occurring in the darolutamide arm were reported as SAEs. No treatment discontinuations, interruptions or reductions were required due to seizure event in either arm.

Rash

Overall, treatment-emergent events of rash were reported more commonly in patients treated with darolutamide than in those who received placebo (2.94% vs. 0.90%, respectively) with an event rate of 2.1 vs. 0.9 per 100 PY (incidence risk ratio of 2.38) after adjusting for the difference in treatment duration between the treatment arms.

Rash events were reported with worst grade of 1 or 2 in severity in all but 1 darolutamide treated patient (0.1%), who had rash with worst grade of 3 during the study.

No SAEs or permanent study treatment discontinuations due to rash events were reported. Dose interruptions due to rash, rash maculopapular and rash pustular were reported in 1 patient each (0.1%) in the darolutamide arm. Dose reduction was required in 1 patient with rash (0.1%) in the darolutamide arm. No dose modifications due to rash events were reported in the placebo arm.

At the PT level, the main contributor for the observed difference between the treatment arms was the unspecific term rash which was reported in 1.8% vs. 0.7% of patients in the darolutamide and placebo arms, respectively. This was followed by rash maculo-papular (0.4% vs. 0%). Other terms were reported at even lower levels in both treatment arms.

Cardiovascular disorders

Cardiac disorders

The overall incidence of TEAEs in the SOC cardiac disorders was higher in the darolutamide arm compared to placebo arm (11.8% vs. 7.4%, respectively).

The difference was observed across all grades, except for grade 5 TEAEs where the incidence was comparable in the darolutamide arm (1.0% vs. 1.4%, respectively). The overall mortality rate of patients in the study

with reported cause 'cardiovascular disease' was comparable between the darolutamide and placebo arms (1.9% vs. 2.0%, respectively).

TEAEs in the MedDRA HLGTs cardiac arrhythmias (6.71% vs. 3.97%), coronary artery disorders (3.25% vs. 2.53%), and heart failures (1.89% vs. 0.90%) represented the key contributors to the overall count on the SOC level and to the disproportion between darolutamide and placebo treatment arms.

Cardiac arrhythmias

Within the HLGT cardiac arrhythmias, the HLTs cardiac conduction disorders (0.94% darolutamide vs. 0.36% placebo), rate and rhythm disorders NEC (3.35% vs. 1.08%), and supraventricular arrhythmias (3.04% vs. 1.62%) mainly contributed to the overall count and to the disproportion on the HLGT level.

The majority of the events were reported with worst grade of 1 or 2. The most common PTs were atrial fibrillation (2.3% vs. 1.4%), arrhythmia (1.5% vs. 0.5%) and bradycardia (1.0% vs. 0.2%). No difference between the darolutamide and placebo arms, respectively, was observed for HLT ventricular arrhythmias and cardiac arrest (0.6% vs.0.9%).

For analysis of cardiac arrhythmias, the ECG data analysis was considered in addition to the TEAE analysis. In the Phase 1/2 studies in mCRPC patients, no notable changes from baseline in any of the ECG parameters nor dose dependent increases in PR or QTc intervals were observed.

A dedicated analysis of the potential effect of darolutamide on cardiac repolarization performed in a subset of study 17712 did not show any clinically relevant effect on cardiac repolarization (QTc).

Coronary artery disorders and heart failures

The HLGT coronary artery disorders is represented by the HLT coronary artery disorders NEC (1.36% vs. 0.54%) and the HLT ischemic coronary artery disorders (2.52% vs. 1.99%). The majority of the events within the HLGT coronary artery disorders were reported with worst grade of 3 or higher in the darolutamide arm. The most frequent PTs were coronary artery disease (1.0% vs. 0.2%) and angina pectoris (1.3% vs. 0.7%).

The HLGT heart failures contains one HLT heart failures NEC which is mainly represented by a PT cardiac failure (1.4% vs. 0.9%).

Ischaemic heart disease

Ischaemic heart disease occurred in 3.2% of patients treated with darolutamide and in 2.5% of patients treated with placebo. Grade 5 events occurred in 0.3% of patients treated with darolutamide and 0.2% of patients treated with placebo.

Cerebrovascular disorders

TEAEs were reported at a similar level in the HLGT CNS vascular disorders in the darolutamide arm (1.68%) compared to placebo arm (1.81%). TEAEs in the grouped terms of cerebral ischemia (1.36% vs. 1.44%) and cerebral and intracranial haemorrhage (0.21% vs. 0.36%) did not occur at a higher incidence in darolutamide arm.

The cause of death was reported as 'cerebrovascular disease' in 0.2% vs. 0.9% of patients in the darolutamide and placebo arms, respectively.

Hypertension

The reported PTs for the MLG 'hypertension' included blood pressure increased, blood pressure systolic increased, essential hypertension, and hypertension.

Treatment-emergent events of hypertension occurred in 7.34% of patients in the darolutamide arm and in 5.96% of patients in the placebo arm. The incidence was similar between darolutamide and placebo arms (5.2 vs. 5.8 per 100 PY, respectively, with an incidence risk ratio of 0.90) after adjusting for the duration of treatment.

Hypertension with grade 3 as the worst grade was experienced by 3.4% and 2.3% of patients in the darolutamide and placebo arms, respectively (reported mostly as PT 'hypertension'). No grade 4 events of hypertension were reported.

Interval-specific and cumulative event rates and prevalence rates for hypertension events did not reveal any meaningful differences between the treatment arms.

No notable differences between the treatment arms were observed in the mean and median blood pressure measurement values over time.

Vasodilatation and flushing

The reported PTs for the MLG 'vasodilatation and flushing' included flushing and hot flush. Events of vasodilatation and flushing were reported in 5.66% of patients in the darolutamide arm and in 4.15% of patients in the placebo arm. The results were comparable between darolutamide and placebo arms (4.0 vs. 4.1 per 100 PY, respectively, with an incidence risk ratio of 1.0) after adjusting for the difference in treatment duration.

While no meaningful differences were seen in the cumulative incidence of these events a slight difference was noted in the interval incidence and prevalence rates in favour of the placebo arm.

No permanent treatment discontinuations due to flushing or hot flushes were observed in the study. Treatment interruption due to flushing was reported in 1 patient (0.1%) and dose reduction due to hot flush in 2 patients (0.2%) in the darolutamide arm.

Diabetes mellitus and hyperglycaemia

No differences were observed in the incidence of diabetes mellitus and hyperglycaemia events between the darolutamide and placebo treatment arms (2.31% vs. 2.17%, respectively). After adjusting for the treatment duration, the rates were 1.6 vs. 2.1 per 100 PY, respectively, with an incidence risk ratio of 0.78. No routine monitoring of blood glucose values was performed in study 17712.

Mental impairment disorders

The incidence of mental impairment disorders at the HLGT level was comparable between darolutamide and placebo treatment arms (1.68% vs. 1.81%, respectively). After adjusting for the treatment duration, the rates were 1.2 vs. 1.7 per 100 PY, respectively, with an incidence risk ratio of 0.68.

This was followed by HLT mental impairment (excluding dementia and memory loss) (0.42% darolutamide vs. 0.36% placebo); and includes PTs cognitive disorder (0.4% vs. 0.2%) and disturbance in attention (0% vs. 0.2%)

TEAEs were reported only in the darolutamide treatment arm in the HLT dementia (excluding Alzheimer's type) (0.52% of patients) and HLT Alzheimer's disease (including subtypes) (0.10% of patients), and

included the following PTs: dementia (0.2% darolutamide vs. 0% placebo), senile dementia (0.2% vs. 0%) and vascular dementia (0.1% vs. 0%) and dementia Alzheimer's type (0.1% vs. 0%).

Depressed mood disorders

The reported PTs for HLGT 'depressed mood disorders and disturbances' included depression and depressed mood. The incidence of depressed mood disorders at the HLGT level was comparable between darolutamide and placebo treatment arms (1.78% vs. 1.44%, respectively). After adjusting for the treatment duration, the rates were 1.3 vs. 1.4 per 100 PY, respectively, with an incidence risk ratio of 0.90.

Most of the events were reported under PT depression (1.7% vs. 1.3%, respectively) while PT depressed mood was reported in 1 patient each in both darolutamide (0.1%) and placebo (0.2%) arms. There were no reports concerning suicidality.

Breast disorders/gynecomastia

The incidence of breast disorders/gynecomastia events was 2.31% in the darolutamide arm and 1.62% in the placebo arm in study 17712. After adjusting for the treatment duration, the rates were comparable, 1.6 vs. 1.6 per 100 PY, respectively, with an incidence risk ratio of 1.04

At the PT level, though, a slight difference was seen in the incidence of gynecomastia between patients treated with darolutamide (2.0%) compared to patients receiving placebo (1.1%).

There were no permanent treatment discontinuations or dose interruptions due to PT gynecomastia in the darolutamide arm. For one patient (0.1%) in the darolutamide arm the drug dose was reduced due to gynecomastia.

Adverse drug reactions

Integrated Analysis database and clinical database for study 17712 were used for analysis of the safety data from the completed clinical studies in prostate cancer patients in the metastatic CRPC pool (n=173) and the non-metastatic CRPC pool (n=1508); cut-off date 03 SEP 2018.

The MAH database was used complementary for analysis on individual patient level (i.e. narrative review); cut-off date 03 SEP 2018.

For identification and labeling of the adverse drug reactions, the MedDRA preferred terms (PTs) of the treatment-emergent adverse events (TEAEs) were reviewed and when appropriate were organised into groups of clinically synonymous or pathophysiologically related terms.

The identification of the adverse drug reactions was performed in a stepwise approach:

1) Selection of the TEAE preferred or grouped terms by: a. Evidence of disproportionality / imbalance between the treatment arms; Selection as "special topic" i.e. terms / disorders considered as potential risks or known to be associated with androgen deprivation therapy (ADT) or with novel anti-androgens;

2) Analysis of selected TEAE terms for evidence (supportive and refuting)

3) Assessment of relevance of the prioritized TEAE term / medical concept

Besides the analysis of TEAEs, summary tabulations for laboratory test and vital signs values were reviewed for central tendency (mean and median values) over time and abnormal values distribution (categorized by severity grade) including shift-from-baseline analysis.

Table 35: Adverse drug reactions reported in patients treated with Nubeqa

System Organ Class Preferred Term	Nubeqa (n=954)		Placebo (n=554)	
	All Grades	Grade 3-4	All	Grade 3-4
Cardiac Disorders				
Heart failure *	1.9%	0.5%	0.9%	0%
Ischaemic heart disease*(b)	3.2%	1.7%	2.5%	0.4%
Musculoskeletal And Connective Tissue Disorders				
Pain in Extremity	5.8%	0.0%	3.2%	0.2%
Musculoskeletal pain **	3.9%	0.1%	2.0%	0.2%
Fractures ***	4.2%	0.9%	3.6%	0.9%
Skin and subcutaneous tissue disorders				
Rash	2.9%	0.1%	0.9%	0%
General disorders and administration site conditions				
Fatigue/asthenic conditions	15.8%	0.6%	11.4%	1.1%

* Per SOC/ HLGT/ HLT/ PT
** PT
*** grouping terms
(b) Coronary artery disorders

Table 36: Laboratory test abnormalities related to Nubeqa treatment

Laboratory parameter (in % of samples investigated)	Nubeqa (n=954)*		Placebo (n=554)*	
	All Grades**	Grade 3/4**	All Grades**	Grade 3/4**
Blood and lymphatic system disorders				
Neutrophil count decreased	19.6%	3.5%	9.4%	0.5%
Hepatobiliary disorders				
Bilirubin increased	16.4%	0.1%	6.9%	0%
AST increased	22.5%	0.5%	13.6%	0.2%

* The number of patients tested for a specific laboratory test parameter may be different. The incidence of each laboratory test abnormality was calculated accordingly.

** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only laboratory test values (no clinical assessments) were used for the grading. Grade 4 laboratory test values were limited to neutrophil count decreased.

Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)

Treatment-emergent SAEs in nmCRPC study 17712

Overall, treatment-emergent SAEs were reported in 24.8% of patients in the darolutamide arm and in 20.0% of patients in the placebo arm in study 17712. More than half of these patients had an SAE with worst grade of 3 in severity, with an incidence rate of 13.8% and 11.0% in the darolutamide and placebo arms, respectively. SAEs with worst grade of 4 were experienced by 2.0% of patients in the darolutamide arm and 1.6% of patients in the placebo arm. Most SAEs were reported in <1% of patients in both treatment arms. The SAEs occurring in ≥1% of patients in either darolutamide or placebo arm, respectively, were urinary retention (1.6% vs. 3.2%), pneumonia (1.4% vs. 1.1%) and haematuria: (1.0% vs. 1.1%).

Table 37: Incidence of treatment-emergent SAEs (any grade) by MedDRA PT occurring in >2 patients in either arm in nmCRPC study 17712 (SAF)

	Darolutamide	Placebo
MedDRA PT Version 21.0	N = 954 n (%)	N = 554 n (%)
Any treatment-emergent SAE	**237 (24.8%)**	**111 (20.0%)**
Urinary retention	15 (1.6%)	18 (3.2%)
Pneumonia	13 (1.4%)	6 (1.1%)
Haematuria	10 (1.0%)	6 (1.1%)
Atrial fibrillation	8 (0.8%)	3 (0.5%)
Cardiac failure	8 (0.8%)	4 (0.7%)
Urinary tract infection	7 (0.7%)	0
Urinary tract obstruction	6 (0.6%)	2 (0.4%)
Acute myocardial infarction	5 (0.5%)	0
Ischaemic stroke	5 (0.5%)	2 (0.4%)
Pulmonary embolism	5 (0.5%)	1 (0.2%)
Acute kidney injury	4 (0.4%)	3 (0.5%)
Angina pectoris	4 (0.4%)	2 (0.4%)
Death	4 (0.4%)	1 (0.2%)
Decreased appetite	4 (0.4%)	0
Dyspnoea	4 (0.4%)	1 (0.2%)
General physical health deterioration	4 (0.4%)	0
Intestinal obstruction	4 (0.4%)	0
Myocardial infarction	4 (0.4%)	2 (0.4%)
Bladder neoplasm	3 (0.3%)	0
Chest pain	3 (0.3%)	0
Colon cancer	3 (0.3%)	0
Fall	3 (0.3%)	1 (0.2%)
Hydronephrosis	3 (0.3%)	3 (0.5%)
Hyperglycaemia	3 (0.3%)	1 (0.2%)
Osteoarthritis	3 (0.3%)	1 (0.2%)
Pancreatic carcinoma	3 (0.3%)	0
Pyelonephritis	3 (0.3%)	0
Cardiac arrest	2 (0.2%)	3 (0.5%)
Cerebrovascular accident	2 (0.2%)	3 (0.5%)
Chronic obstructive pulmonary disease	2 (0.2%)	3 (0.5%)
Dysuria	1 (0.1%)	3 (0.5%)
Renal failure	1 (0.1%)	4 (0.7%)

MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; PT = Preferred term; SAE = Serious adverse event; SAF = Safety analysis set

Note: A patient may have more than one entry.

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.2/1 and Table 14.3.2/2

Deaths

Table 38: Overview of deaths in nmCRPC study 17712 (SAF)

	Darolutamide	Placebo
	N = 954 n (%)	N = 554 n (%)
All deaths	**79 (8.3%)**	**58 (10.5%)**
Death during first to last dose of study drug	14 (1.5%)	7 (1.3%)
Deaths up to 30 days after last dose of study drug	21 (2.2%)	11 (2.0%)
Deaths later than 30 days after last dose of study drug	44 (4.6%)	40 (7.2%)

N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; SAF = Safety analysis set

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.2/12

The most common cause of death in both darolutamide and placebo arms was prostate cancer (3.1% vs. 4.5% of all patients, respectively), followed by 'other specify' (2.4% vs. 1.8%), and cardiovascular disease (1.9% vs. 2.0%).

Table 39: Causes of deaths in nmCRPC study 17712 (SAF)

		Darolutamide		Placebo	
		Total N = 954 n (%)	All deaths N = 79 [a] n (%)	Total N = 554 n (%)	All deaths N = 58 [a] n (%)
All deaths		**79 (8.3%)**	**79 (100%)**	**58 (10.5%)**	**58 (100%)**
Cause of death:	Prostate cancer	30 (3.1%)	30 (38.0%)	25 (4.5%)	25 (43.1%)
	Other, specify	23 (2.4%)	23 (29.1%)	10 (1.8%)	10 (17.2%)
	Cardiovascular disease	18 (1.9%)	18 (22.8%)	11 (2.0%)	11 (19.0%)
	Respiratory disease	5 (0.5%)	5 (6.3%)	6 (1.1%)	6 (10.3%)
	Cerebrovascular disease	2 (0.2%)	2 (2.5%)	5 (0.9%)	5 (8.6%)
	Other cancer	1 (0.1%)	1 (1.3%)	0 (0.0%)	0
	Diabetes	0 (0.0%)	0	1 (0.2%)	1(1.7%)

N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; SAF = Safety analysis set

a: Percentages in this column were manually calculated from the total number of patients who died.

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.2/12

Grade 5 TEAEs

Grade 5 TEAEs occurred in 3.9% of patients in the darolutamide arm and in 3.2% of patients in the placebo arm. Grade 5 TEAEs that were reported in more than 1 patient were death (0.4%), cardiac failure (0.3%), and cardiac arrest, general physical health deterioration, and pulmonary embolism (0.2% each) in the darolutamide arm; and cardiac failure and cardiac arrest (0.5% each), and acute respiratory failure (0.4%) in the placebo arm.

Grade 5 TEAEs that were considered drug-related by the investigator occurred in 0.1% of patients in the darolutamide arm (1 patient with small intestinal perforation) and 0.4% of patients in the placebo arm (1 patient with myocardial infarction and intracranial haemorrhage each.

Laboratory findings

Haematological and biochemical laboratory values

Table 40: CTCAE grades for abnormal haematological and biochemical laboratory values with incidence rate >5%: Worst grade after start of treatment in nmCRPC study 17712 (SAF)

	Darolutamide n (%)						Placebo n (%)					
		Worst CTCAE toxicity grade						Worst CTCAE toxicity grade				
Event category [b] CTCAE term (version 4.03)	N [a]	Grade 1-4	Grade 1	Grade 2	Grade 3	Grade 4	N [a]	Grade 1-4	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders												
Anemia	817 (100.0)	817 (100.0)	745 (91.2)	65 (8.0)	7 (0.9)	0	426 (100.0)	426 (100.0)	395 (92.7)	26 (6.1)	5 (1.2)	0
Investigations												
Alanine aminotransferase increased	947 (100.0)	79 (8.3)	73 (7.7)	3 (0.3)	3 (0.3)	0	552 (100.0)	38 (6.9)	36 (6.5)	1 (0.2)	1 (0.2)	0
Alkaline phosphatase increased	952 (100.0)	52 (5.5)	47 (4.9)	4 (0.4)	1 (0.1)	0	552 (100.0)	46 (8.3)	37 (6.7)	7 (1.3)	2 (0.4)	0
Aspartate aminotransferase increased	952 (100.0)	214 (22.5)	206 (21.6)	3 (0.3)	5 (0.5)	0	552 (100.0)	75 (13.6)	73 (13.2)	1 (0.2)	1 (0.2)	0
Blood bilirubin increased	951 (100.0)	156 (16.4)	113 (11.9)	42 (4.4)	1 (0.1)	0	552 (100.0)	38 (6.9)	31 (5.6)	7 (1.3)	0	0
Creatinine increased	952 (100.0)	271 (28.5)	207 (21.7)	58 (6.1)	5 (0.5)	1 (0.1)	552 (100.0)	158 (28.6)	126 (22.8)	27 (4.9)	2 (0.4)	3 (0.5)
Lymphocyte count decreased	951 (100.0)	503 (52.9)	334 (35.1)	135 (14.2)	32 (3.4)	2 (0.2)	552 (100.0)	259 (46.9)	167 (30.3)	73 (13.2)	19 (3.4)	0
Neutrophil count decreased	951 (100.0)	186 (19.6)	72 (7.6)	81 (8.5)	24 (2.5)	9 (0.9)	552 (100.0)	52 (9.4)	26 (4.7)	23 (4.2)	1 (0.2)	2 (0.4)
Platelet count decreased	951 (100.0)	181 (19.0)	178 (18.7)	1 (0.1)	1 (0.1)	1 (0.1)	551 (100.0)	91 (16.5)	89 (16.2)	1 (0.2)	1 (0.2)	0
White blood cell decreased	951 (100.0)	187 (19.7)	83 (8.7)	93 (9.8)	10 (1.1)	1 (0.1)	552 (100.0)	65 (11.8)	36 (6.5)	23 (4.2)	6 (1.1)	0
Metabolism and nutrition disorders												
Hypocalcemia	952 (100.0)	184 (19.3)	178 (18.7)	6 (0.6)	0	0	552 (100.0)	92 (16.7)	84 (15.2)	8 (1.4)	0	0
Hyponatremia	952 (100.0)	117 (12.3)	102 (10.7)	0	14 (1.5)	1 (0.1)	552 (100.0)	70 (12.7)	64 (11.6)	0	6 (1.1)	0
Hypercalcemia	946 (100.0)	80 (8.5)	80 (8.5)	0	0	0	550 (100.0)	61 (11.1)	60 (10.9)	1 (0.2)	0	0
Hyperkalemia	951 (100.0)	192 (20.2)	139 (14.6)	42 (4.4)	6 (0.6)	5 (0.5)	552 (100.0)	93 (16.8)	65 (11.8)	21 (3.8)	5 (0.9)	2 (0.4)
Hypernatremia	941 (100.0)	64 (6.8)	63 (6.7)	1 (0.1)	0	0	549 (100.0)	32 (5.8)	30 (5.5)	0	0	2 (0.4)

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; INR = International normalized ratio; N = Total number of patients; n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; SAF = Safety analysis set.

a: Number of patients with a specific laboratory value available. It does not include 'not graded'.

b: The requirement for monitoring the prothrombin time (expressed as INR) was removed in protocol amendment 2 (see Module 5.3.5.1, Report PH-39723, Section 16.1.1). The measurement was not performed for most patients and therefore associated laboratory abnormalities (increased INR) are not presented in this table.

Note: A patient was considered at risk for toxicity if the patient had laboratory measurement for the toxicity.

Denominator and rates for each laboratory is the number of patients with specific laboratory value available.

Only laboratory values (no clinical assessments) were used for the grading.

Laboratory toxicities reported as AEs that include clinical assessments can be found in AE tables.

If the reference ranges or other information necessary to derive grades are unavailable or result has a special character (such as > or <) then the grade is set to 'not graded'. In the event of overlapping CTCAE criteria ranges for specific laboratory tests, the algorithm assigns the higher grade.

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.4/3

Neutrophil count decreased was reported as a laboratory abnormality in 19.6% of patients treated with darolutamide and in 9.4% of patients treated with placebo. The median time to nadir was 256 days. The laboratory tests abnormalities manifested predominantly as grade 1 or 2 intensity. Neutrophil count decreased of grade 3 and 4 was reported in 3.5% and 0.5% of patients, respectively. Only one patient permanently discontinued darolutamide due to neutropenia. Neutropenia was either transient or reversible (88% of patients) and were not associated with any clinically relevant signs or symptoms.

Bilirubin increased was reported as a laboratory abnormality in 16.4% of patients treated with darolutamide and in 6.9% of patients treated with placebo. The episodes were predominantly of grade 1 or 2 intensity, not associated with any clinically relevant signs or symptoms, and reversible after darolutamide was discontinued. Bilirubin increased of grade 3 was reported in 0.1% of patients treated with darolutamide and in 0% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased bilirubin was 152.8 days, and the mean duration of the first episode was 182.4 days. No patients were discontinued from treatment due to increase in bilirubin.

AST increased was reported as a laboratory abnormality in 22.5% of patients treated with darolutamide and in 13.6% of patients treated with placebo. The episodes were predominantly of grade 1 or 2 intensity, not associated with any clinically relevant signs or symptoms, and reversible after darolutamide was discontinued. AST increased of grade 3 was reported in 0.5% of patients treated with darolutamide and in

0.2% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased AST was 257.8 days, and the mean duration of the first episode was 117.8 days. No patients were discontinued from treatment due to increase in AST.

Vital signs, physical findings and other observations related to safety

No differences were observed between the treatment arms in the changes of mean and median values over time for blood pressure measurements, body weight, BMI, and heart rate.

Electrocardiograms

At screening for study 17712, a 12-lead ECG was performed for all 954 and 554 patients in the darolutamide and placebo arm, respectively, of which 56.2% and 56.1% of patients had central baseline ECG reading interpreted as abnormal and thus at baseline, ECG findings were considered comparable between groups. There were no notable treatment arm differences with respect to the proportion of patients with changes in QTc from baseline or the proportion of patients with QTc interval prolongation. The analysis of the ECG data over time (by visit) did not reveal any relevant imbalance between the treatment arms nor changes from baseline. This suggests that darolutamide has no clinically meaningful effect on the cardiac electrical conduction system, ectopic activity, cardiac rhythm and ST segment.

Cardiovascular Safety Expert Report: ECG/PK Substudy of 17712 in nmCRPC patients

A dedicated analysis of the potential effect of darolutamide on cardiac repolarization was performed in a PK subset of the Phase 3 study 17712 (ARAMIS). These patients had baseline ECGs and at least one triplicate ECG collection during darolutamide/placebo treatment, time matched to a PK sample. The PK samples covered the entire PK profile of darolutamide, including C_{max}.

The primary objective of this analysis was a concentration-QTc modelling approach assessing the effect of darolutamide concentration on cardiac repolarization.

As secondary objectives, central tendency analyses supplemented by exploratory outlier and morphology analyses were performed. For the central tendency analysis, the endpoint 'change from baseline' was used in a 'time averaged' analysis and a 'time point' analysis.

The time point analysis was performed for different post start-of-treatment time points/visits ('by visit') as well as for stratified time intervals from the last dose of study treatment ('time post administration'). Primary and secondary objectives were investigated in slightly different subsets. The concentration-QTc effect was analysed in 323 patients receiving darolutamide and in 177 patients receiving placebo. The central tendency analysis was performed in 337 and 183 patients, respectively. As there was no evidence that darolutamide exposure has an effect on heart rate the final assessment on cardiac repolarization focused on QTcF for all analyses.

The concentration-QTcF relationship of darolutamide and the single analytes, (S,S)-darolutamide, (S,R)-darolutamide and keto-darolutamide, could be described by a predefined linear concentration-QTc effect model. The slopes of the concentration-QTcF relationship were negative for all three single analytes when estimated using the single analyte models. The upper limit of the 95% one-sided confidence interval of the estimated difference in QTcF from baseline and placebo (ΔΔQTcF) did not exceed the threshold of 10 ms based on the prediction of the single analyte models. The outcome did not change when a combined concentration-QTcF model for all three analyses was used.

The central tendency analyses did not provide a clear signal of any effect of darolutamide on heart rate, AV conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were relatively balanced rates of new clinically relevant morphological changes in the darolutamide and placebo arms, except for a higher incidence of atrial fibrillation and atrial flutter in the darolutamide treatment arm, although 50% of these patients (3 of 6 patients in the darolutamide treatment arm) had a prior history of atrial tachyarrhythmias

There was also no signal of any effect of darolutamide on cardiac repolarization as evidenced by the results of the by time point analysis. For the 'by visit' analysis with more than 200 patients per time point, the upper limit of the 95% one-sided confidence interval of the placebo-corrected QTcF change from baseline was less than 1.0 ms. For the 'time post administration' analysis with more than 90 patients per time point, the upper limit of the 95% one-sided confidence interval did not exceed 5 ms at any time. The results of the time-averaged and outlier analyses are further confirmatory evidence that darolutamide has no effect on cardiac repolarization.

In patients not belonging to the PK subset, single ECGs instead of triplicate ECGs were collected with exception of the baseline value. The proportion of patients with QTc prolongation of >480 ms or >500 ms was similar in the subset and in the total safety population. No notable differences were seen in the proportion of patients with normal and abnormal 12-lead ECG readings at visits during treatment compared to baseline. There were also no notable differences between the treatment arms with respect to the proportion of patients with changes in QTc from baseline or the proportion of patients with QTc interval prolongation).

Safety in special populations

Age

In nmCRPC patients in study 17712, the results of population PK analysis (study 18651, PK subset of study 17712 analysed by four age groups showed a significantly increased exposure [AUC(0 12)ss] to darolutamide with increasing age. An approximately 1.6 fold difference of geometric mean and median exposure was observed between patients of ≥85 years and patients in the <65 years age group.

Table 41: Overview of TEAEs by age in nmCRPC study 17712 (SAF)

	Darolutamide				Placebo			
	Age (years)				Age (years)			
	<65	65-74	75-84	≥85	<65	65-74	75-84	≥85
Number of patients (%) with:	**N = 113** n (%)	**N = 373** n (%)	**N = 383** n (%)	**N = 85** n (%)	**N = 84** n (%)	**N = 216** n (%)	**N = 209** n (%)	**N = 45** n (%)
Any TEAE, worst grade:	93 (82.3)	310 (83.1)	321 (83.8)	70 (82.4)	67 (79.8)	156 (72.2)	163 (78.0)	40 (88.9)
Grade 1	41 (36.3)	83 (22.3)	86 (22.5)	9 (10.6)	22 (26.2)	55 (25.5)	44 (21.1)	13 (28.9)
Grade 2	29 (25.7)	135 (36.2)	107 (27.9)	31 (36.5)	31 (36.9)	63 (29.2)	58 (27.8)	14 (31.1)
Grade 3	21 (18.6)	75 (20.1)	94 (24.5)	25 (29.4)	11 (13.1)	31 (14.4)	49 (23.4)	8 (17.8)
Grade 4	1 (0.9)	7 (1.9)	12 (3.1)	1 (1.2)	1 (1.2)	2 (0.9)	5 (2.4)	1 (2.2)
Grade 5 (death/fatal)	1 (0.9)	10 (2.7)	22 (5.7)	4 (4.7)	2 (2.4)	5 (2.3)	7 (3.3)	4 (8.9)
Serious TEAE	21 (18.6)	79 (21.2)	109 (28.5)	28 (32.9)	10 (11.9)	36 (16.7)	51 (24.4)	14 (31.1)
Fatal (grade 5)	1 (0.9)	10 (2.7)	22 (5.7)	4 (4.7)	2 (2.4)	5 (2.3)	7 (3.3)	4 (8.9)
Requires or prolongs hospitalization	20 (17.7)	72 (19.3)	93 (24.3)	24 (28.2)	7 (8.3)	30 (13.9)	46 (22.0)	14 (31.1)
Life-threatening	1 (0.9)	9 (2.4)	18 (4.7)	1 (1.2)	0 (0.0)	6 (2.8)	7 (3.3)	3 (6.7)
Disability/incapacity	0 (0.0)	1 (0.3)	3 (0.8)	1 (1.2)	0 (0.0)	2 (0.9)	3 (1.4)	1 (2.2)
Other (medically significant)	4 (3.5)	21 (5.6)	14 (3.7)	5 (5.9)	2 (2.4)	10 (4.6)	9 (4.3)	1 (2.2)
TEAE leading to dose modification [a]	6 (5.3)	42 (11.3)	71 (18.5)	16 (18.8)	6 (7.1)	17 (7.9)	21 (10.0)	8 (17.8)
TEAE leading to permanent discontinuation of study drug	7 (6.2)	22 (5.9)	42 (11.0)	14 (16.5)	5 (6.0)	12 (5.6)	23 (11.0)	8 (17.8)
Specific categories								
Psychiatric disorders (SOC)	9 (8.0)	26 (7.0)	19 (5.0)	3 (3.5)	6 (7.1)	9 (4.2)	9 (4.3)	4 (8.9)
Nervous system disorders (SOC)	11 (9.7)	56 (15.0)	64 (16.7)	16 (18.8)	10 (11.9)	20 (9.3)	36 (17.2)	8 (17.8)
Accidents and injuries (SMQ)	7 (6.2)	42 (11.3)	45 (11.7)	9 (10.6)	3 (3.6)	12 (5.6)	19 (9.1)	8 (17.8)
Cardiac disorders (SOC)	11 (9.7)	37 (9.9)	53 (13.8)	12 (14.1)	4 (4.8)	11 (5.1)	20 (9.6)	6 (13.3)
Vascular disorders (SOC)	23 (20.4)	63 (16.9)	54 (14.1)	12 (14.1)	13 (15.5)	19 (8.8)	30 (14.4)	6 (13.3)
Central nervous system vascular disorders (SMQ)	2 (1.8)	4 (1.1)	10 (2.6)	2 (2.4)	0 (0.0)	2 (0.9)	7 (3.3)	3 (6.7)
Anticholinergic syndrome (SMQ) [b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Infections and infestations (SOC)	17 (15.0)	98 (26.3)	86 (22.5)	26 (30.6)	13 (15.5)	47 (21.8)	51 (24.4)	9 (20.0)
Quality of life decreased (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	9 (8.0)	38 (10.2)	51 (13.3)	11 (12.9)	5 (6.0)	19 (8.8)	27 (12.9)	9 (20.0)

AE = Adverse event; N = Total number of patients (100%); n = Number of patients with event; MedDRA = Medical Dictionary for Regulatory Activities; nmCRPC = Non-metastatic castration-resistant prostate cancer; PT = Preferred term; SAF = Safety analysis set; SMQ = Standardized MedDRA Query; SOC = System organ class; TEAE = Treatment-emergent adverse event

a: Modifications include dose interruptions and reductions.

b: The algorithm approach was used per MedDRA guidance on the SMQ Anticholinergic syndrome.

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.1.2/1 to Table 14.3.1.2/4 and Table 14.3/1s2.

Race/Ethnicity

No dedicated analysis of safety data on ethnic differences was performed. A subgroup analysis by geographical region (North America, Asia Pacific, ROW) were done in study 17712. There was no meaningful difference in the incidence of TEAEs between the geographical regions or between the treatment arms.

Body weight

Based on the population PK analysis there was almost no effect of body weight on the PK of darolutamide for patients with body weight between 75kg to≥90 kg and a comparable AUC(0 12)ss was seen in patients in body weight categories 75 to <80 kg, 80 to <90 kg and ≥90 kg. Of note, a relatively higher median AUC value was observed in the subgroup <75 kg.

Renal Impairment

Higher incidences of grade 5 events, TEAEs leading to dose modification or permanent treatment discontinuation were observed in both darolutamide and placebo treatment arms as renal function worsened.

Table 42: Overview of TEAEs by renal function at baseline in nmCRPC study 17712 (SAF)

		Darolutamide			Placebo		
		eGFR at baseline			eGFR at baseline		
		Normal	Mildly impaired	Moderately/ severely [a] impaired	Normal	Mildly impaired	Moderately/ severely [a] impaired
Number of patients (%) with		N = 412 n (%)	N = 422 n (%)	N = 120 n (%)	N = 230 n (%)	N = 248 n (%)	N = 76 n (%)
Any TEAE		342 (83.0)	350 (82.9)	102 (85.0)	178 (77.4)	182 (73.4)	66 (86.8)
Worst grade:	Grade 1	105 (25.5)	88 (20.9)	26 (21.7)	67 (29.1)	53 (21.4)	14 (18.4)
	Grade 2	132 (32.0)	136 (32.2)	34 (28.3)	77 (33.5)	65 (26.2)	24 (31.6)
	Grade 3	87 (21.1)	98 (23.2)	30 (25.0)	27 (11.7)	56 (22.6)	16 (21.1)
	Grade 4	10 (2.4)	8 (1.9)	3 (2.5)	0 (0.0)	4 (1.6)	5 (6.6)
	Grade 5 (death)	8 (1.9)	20 (4.7)	9 (7.5)	7 (3.0)	4 (1.6)	7 (9.2)
SAE		89 (21.6)	109 (25.8)	39 (32.5)	36 (15.7)	51 (20.6)	24 (31.6)
TEAE leading to dose modification [b]		50 (12.1)	59 (14.0)	26 (21.7)	13 (5.7)	26 (10.5)	13 (17.1)
TEAE leading to permanent discontinuation of study drug		20 (4.9)	47 (11.1)	18 (15.0)	11 (4.8)	23 (9.3)	14 (18.4)
Any drug-related TEAE [c]		112 (27.2)	113 (26.8)	33 (27.5)	44 (19.1)	51 (20.6)	15 (19.7)
Worst grade:	Grade 1	54 (13.1)	65 (15.4)	13 (10.8)	29 (12.6)	30 (12.1)	9 (11.8)
	Grade 2	43 (10.4)	40 (9.5)	15 (12.5)	12 (5.2)	11 (4.4)	3 (3.9)
	Grade 3	11 (2.7)	8 (1.9)	5 (4.2)	3 (1.3)	9 (3.6)	2 (2.6)
	Grade 4	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 5 (death)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.3)
Drug-related SAE		7 (1.7)	1 (0.2)	2 (1.7)	1 (0.4)	4 (1.6)	1 (1.3)
Drug-related TEAE leading to dose modification [b]		22 (5.3)	18 (4.3)	9 (7.5)	3 (1.3)	7 (2.8)	4 (5.3)
Drug-related TEAE leading to permanent discontinuation of study drug		4 (1.0)	8 (1.9)	3 (2.5)	2 (0.9)	8 (3.2)	3 (3.9)

eGFR = estimated glomerular filtration rate; N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; SAE = Serious adverse event; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event

a: There was 1 patient with severely impaired renal function in the darolutamide arm, and no patients in the placebo arm with severely impaired renal function (see Table 1–12). No patients had end stage renal disease.

b: Modifications include dose interruptions and reductions.

c: Based on investigator's assessment.

Source: Module 5.3.5.1, Report PH-39723, Table 14.3.1.3/1 to Table 14.3.1.3/3

In the mCRPC pool, the number of patients in the moderately impaired renal function group was lower (N=16) compared to the other renal function groups. The overall incidences of TEAEs were comparable across the renal function groups. However, Grade 5 TEAEs, SAEs and dose modifications occurred more commonly in the moderately impaired renal function group.

Hepatic impairment

There were no patients with severe hepatic impairment at baseline. Two patients in the darolutamide arm and 1 patient in the placebo arm had moderately impaired hepatic function.

The number of patients in both darolutamide and placebo arms, respectively, was lower in the mildly (N=89 and N=43) and moderately (N=2 and N=1) impaired hepatic function groups compared to the normal hepatic function group.

No meaningful differences were observed between the hepatic function groups or treatment arms in the overall incidence of TEAEs, or in the incidence of TEAEs with worst grade of 3, 4 or 5.

There was no clinically meaningful difference in the incidence of TEAEs between the hepatic function groups or between the treatment arms.

Discontinuation due to adverse events

TEAEs leading to permanent discontinuation of study drug

In the nmCRPC population, the percentage of subjects with treatment discontinuation was comparable between the two arms, 8.9% in the darolutamide arm compared to 8.7% in placebo arm. All TEAEs leading to study discontinuation occurred at low rates <1%. Except for cardiac failure (0.4% darolutamide vs. 0.7% placebo) and death (0.4% vs. 0.2%), all other TEAEs resulting in permanent treatment discontinuation occurred in 1 or 2 patients each in either arm. There was no significant TEAEs in a particular SOC that could be considered causative for treatment discontinuation.

Table 43: Incidence of TEAEs leading to permanent discontinuation of study drug in nmCRPC study 17712 (SAF)

		Darolutamide	Placebo
		N = 954 n (%)	N = 554 n (%)
Any TEAE leading to permanent discontinuation		**85 (8.9%)**	**48 (8.7%)**
Worst CTCAE grade:	Grade 1	1 (0.1%)	2 (0.4%)
	Grade 2	23 (2.4%)	8 (1.4%)
	Grade 3	22 (2.3%)	19 (3.4%)
	Grade 4	10 (1.0%)	5 (0.9%)
	Grade 5 (death)	29 (3.0%)	14 (2.5%)
TEAEs (any grade) occurring in >1 patient in either arm by MedDRA PT (v. 21.0)			
Cardiac failure		4 (0.4%)	4 (0.7%)
Death		4 (0.4%)	1 (0.2%)
Abdominal pain		2 (0.2%)	0
Blood creatinine increased		2 (0.2%)	0
Cardiac arrest		2 (0.2%)	2 (0.4%)
Cerebral infarction		2 (0.2%)	0
Diarrhoea		2 (0.2%)	0
General physical health deterioration		2 (0.2%)	0
Ischaemic stroke		2 (0.2%)	2 (0.4%)
Pancreatic carcinoma		2 (0.2%)	0
Pneumonia		2 (0.2%)	0
Pulmonary embolism		2 (0.2%)	1 (0.2%)
Acute respiratory failure		1 (0.1%)	2 (0.4%)
Cerebrovascular accident		0	2 (0.4%)
Hypertension		0	2 (0.4%)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients (100%); n = Number of patients with event; nmCRPC = Non-metastatic castration-resistant prostate cancer; PT = Preferred term; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event; v. = Version

Note: A patient may have more than one entry.
CTCAE version 4.03.
Source: Module 5.3.5.1, Report PH-39723, Table 14.3.1/17 and Table 14.3.1/18

Adverse events leading to dose interruption or dose reduction

The percentage of patients who had TEAEs that led to dose interruption was higher in the darolutamide arm (12.5%) than in the placebo arm (8.8%) in nmCRPC patients in study 17712.

The most commonly reported TEAEs leading to dose interruption (≥0.5%) in the darolutamide arm were hypertension (darolutamide 0.6% vs. placebo 0%), diarrhoea (0.5% vs. 0.2%) and pneumonia (0.5% vs. 0.4%). Urinary retention was the most common TEAE leading to dose interruption in the placebo arm (darolutamide 0.1% vs. placebo 0.9%) followed by nausea (0.3% vs. 0.5%) and fatigue (0.3% vs. 0.5%).

Dose reduction was required in a higher proportion of patients in the darolutamide arm (4.8%) than in the placebo arm (1.6%) in study 17712.

The most commonly reported TEAEs leading to dose reduction in both darolutamide and placebo arms, respectively, were fatigue (0.7% vs. 0.4%), hypertension (0.3% vs. 0.2%) and nausea (0.3% vs. 0.4%). The rest of the events were experienced by either 1 or 2 patients each in either arm.

Dose was re-escalated (i.e. dose returned to the full dose of 600 mg b.i.d. after dose reduction or delay) in the majority of the patients who had dose modification (for any reason) in both darolutamide and placebo arms (91.7% vs. 88.9% of patients with dose modification, respectively)

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The primary analysis of safety for the proposed indication for treatment of men with nmCRPC at high risk of metastases comes from the pivotal phase 3 Study 17712 (ARAMIS) (n=1508 patients) and is supported by safety data derived from the pooled analysis of Phase 1 and Phase 2 studies in metastatic castration-resistant prostate cancer (mCRPC) patients and from a separate pooled evaluation of safety data from completed Phase 1 studies in non-cancer subjects was also performed (N=101).

Exposure to darolutamide is considered sufficient for the assessment of the safety profile. Median duration of treatment in the pivotal study in nmCRPC at the time of the cut-off was longer in the darolutamide arm than in the placebo arm (14.8 [range: <0.1 to 44.3 months] vs. 11.0 months [range: 0.1 to 40.5 months], respectively). As of the cut-off date 3 September 2018, 64.4% of patients in the darolutamide arm and 36.1% in the placebo arm were still receiving study treatment. Treatment compliance was high for this study with a median of 100% in both arms.

At least one dose modification was required for 15.2% of patients in the darolutamide arm and for 9.7% in the placebo arm. The reason for dose modification was a TEAE in 84.0% of all dose modification events in the darolutamide arm and in 73.1% in the placebo arm. Treatment discontinuations were more common in the placebo arm compared to darolutamide arm (63.9% vs 35.5%, respectively). There were 100 patients with no PSA increase and without documented metastases who discontinued darolutamide treatment. The most frequent reason of treatment discontinuation other than PSA increase or documented metastases was an adverse event in 49.0% of patients, followed by personal reason in 30.0% of patients and judgement of the investigator and protocol deviation in 7.0% each.

In the nmCRPC population in the pivotal study ARAMIS 17712, there was a higher incidence of TEAEs (83.2% vs 76.9%) and drug-related TEAEs (27% vs 19.9%) in the darolutamide arm compared to the placebo arm. Overall the incidence of individual TEAEs was low, with the only TEAE with incidence >10% in both treatment arms being fatigue which was reported in 12.1% and 8.7% of patients in the darolutamide and placebo arms respectively in study ARAMIS 17712.

In study ARAMIS 17712, the most common TEAEs reported with ≥1 percentage point higher incidence in the darolutamide arm compared to placebo arm respectively included: fatigue (12.1% vs 8.7%), diarrhoea (6.9% vs 5.6%), hypertension (6.6 vs 5.2%), pain in extremity (5.8% vs 3.2%), anaemia (5.6% vs. 4.5%), hot flush (5.2% vs. 4.2%), oedema peripheral (4.1% vs. 3.1%), pollakiuria (4.0% vs. 2.9%), headache (3.9% vs. 2.5%), musculoskeletal pain (3.9% vs. 2.0%), dizziness (3.7% vs. 2.5%), weight decreased (3.6% vs. 2.2%), cough (3.0% vs. 2.0%), influenza (2.8% vs. 1.6%), rash (2.9% vs. 0.9%), upper respiratory tract infection (2.6% vs. 1.6%) and pyrexia (2.0% vs. 0.9%).

When adjusted for duration of treatment, there was a higher incidence in the darolutamide arm for the PTs pyrexia, musculoskeletal pain and pain in extremity. Considering that the majority of pyrexia events were reported in close temporal association with bacterial infections and the absence of known association between androgen deprivation and febrile conditions, the observed imbalance in the incidence of pyrexia was not considered to have causal relationship to darolutamide treatment. The observed higher incidence of MedDRA PTs musculoskeletal pain and pain in extremity in the darolutamide vs. the placebo arm provided evidence for causal role for darolutamide in occurrence of these events which were included in the SmPC.

The incidence rates in the darolutamide and placebo arms, respectively, were 2.9% and 0.9% for rash and 15.8% and 11.4% for fatigue/asthenic conditions. Although the incidence of fatigue/asthenic conditions was similar between the treatment arms when adjusted for the difference in treatment duration, the prevalence rate was consistently higher in the darolutamide arm than in the placebo arm. Events of rash and fatigue/asthenic conditions were predominantly reported with worst grade of 1 or 2.

There was a slight but discernible imbalance in the cardiovascular safety profile of darolutamide compared to placebo for cardiac arrhythmias (6.71% vs. 3.97%), coronary artery disorders (3.25% vs. 2.53%), and heart failures (1.89% vs. 0.90%) respectively. In the grouped terms analysis of TEAEs by AE groupings, there was a higher incidence of 'rate and rhythm disorders NEC' seen for darolutamide arm compared to placebo (3.35% vs 1.08% respectively), which even when adjusted for treatment duration continued to show higher risk in darolutamide arm (EAIR 2.4 per 100 PY) vs placebo (EAIR 1.0 per 100 PY) with an incidence risk ratio of 2.27. Even with adjustment for medical history of cardiac disorders, there remains a higher incidence of adverse CV events in the darolutamide arm for coronary artery disorders (1.6% vs 0.6%) and heart failures (1.0% vs 0%).

In the ARAMIS 17712 study, patients with QT prolongation or on medication that could induce prolongation were not excluded. Since androgen deprivation treatment may prolong the QT interval and in line with other products in the class, a warning has been included in section 4.4 of the SmPC. In patients with a history of risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating Nubeqa. The co-administration with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes should be carefully evaluated. These include medicinal products such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, and antipsychotics (e.g. haloperidol) (see SmPC sections 4.4 and 4.5).

There was a slight imbalance in terms of higher incidence of coronary artery disorders for darolutamide compared to placebo. Whilst it is acknowledged there are some structural differences between the three novel androgen receptor inhibitors, the class effect for potentiating a slight increase in ischemic heart disease / coronary artery disorders cannot be overlooked. Therefore, these adverse drug reactions are included in section 4.8 of SmPC.

Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and symptomatic congestive heart failure were excluded from the clinical studies. Therefore, the safety of darolutamide in these patients has not been established. If darolutamide is prescribed, patients with clinically significant cardiovascular disease should be treated for these conditions according to established guidelines (see SmPC section 4.4). Cardiovascular events in patients with significant cardiovascular history will be closely monitored as reflected in the RMP (important potential risk).

Whilst there was no overall imbalance in incidence of hypertension between treatment arms when adjusted for treatment duration (4.7 vs 5.1 EAIR per 100 PY for darolutamide and placebo respectively), there was a higher incidence of Grade 3 hypertension and hypertension requiring dose interruption/reduction in the darolutamide arm compared to the placebo arm. Hypertension will be closely monitored in the PSUR.

There is a plausible mechanism by which androgen receptor inhibition could increase fracture risk. When adjusted for treatment duration between the treatment arms, the rates of fracture were 3.0 vs. 3.5 per 100 PY suggesting comparable rates of fracture and no increase in fracture risk with darolutamide compared to placebo. However, updated data reported that the EAIR was 3.5 vs 3.2 per 100 PY showing a higher incidence with darolutamide. Considering the effect of additional androgen depletion additive to ADT is likely to have increased negative effects on bone mineral density over time, with longer duration of darolutamide + ADT, the risk for fracture is likely to be further increased above placebo + ADT. Therefore, fracture has been included in the SmPC, section 4.8.

In the ARAMIS 17712 study, patients with a history of seizures were not excluded. There was imbalance noted in the baseline history of seizures between arms, however this was weighted against the darolutamide arm which is acceptable in assessing safety. Overall, 13.6% of patients in the ARAMIS study (14.9% in the darolutamide and 11.4% in the placebo arm) used drugs with intermediate or high epileptogenic potential concomitantly to study medication. Approximately 13% of patients were on medication known to lower the seizure threshold and the incidence of seizure remained low.

The incidence of seizure events reported during the study treatment was similar in both treatment arms in study ARAMIS 17712. The events were reported for 2 patients (0.21%) in the darolutamide arm and for 1 patient (0.18%) in the placebo arm. None of the patients with a medical history of seizure experienced a TEAE of seizure in the darolutamide arm. Seizures were reported with worst grade of 1 or 2 in both treatment arms. Based on the clinical data available there is no evidence that treatment with darolutamide would increase the risk for seizures.

The incidence of 'pneumonia and pneumonitis' was 3.25% in the darolutamide arm and 2.17% in the placebo arm and when the analysis was adjusted for difference in treatment duration between the arms there was still a slightly higher rate of pneumonia and pneumonitis in the darolutamide arm compared to placebo, 2.3 vs. 2.1 per 100 PY, respectively, with an incidence risk ratio of 1.10. There were three reported cases of pneumonitis in the darolutamide arm, one case of Grade 1, 2 and 3 each while no case of pneumonitis was reported in the placebo arm. Pneumonitis will be followed in PSUR.

Overall, there was a higher incidence of Grade 3 and 4 AEs reported in darolutamide arm in the pivotal study ARAMIS 17712 in nmCRPC patients: Grade 3 AEs 22.5% vs 17.9% and Grade 4 AEs 2.2% vs 1.6% for darolutamide compared to placebo, respectively. However, most of the Grade 3 AEs occurred at low frequency. Hypertension was the most common Grade 3 AE occurring more commonly in the darolutamide arm compared to placebo arm (3.1% vs 2.2%). Most of the Grade 4 AEs occurred in only 1 patient, except for the following four Grade 4 AEs, acute myocardial infarction, hyperglycaemia, ischemic stroke and respiratory failure, which occurred in 0.2% of patients each in darolutamide arm, with no corresponding events reported in the placebo arm.

In the ARAMIS 17712 study, three Grade 4 AEs were reported under SOC Respiratory, thoracic and mediastinal disorders (mainly respiratory failure and dyspnoea) for patients on darolutamide and two Grade 4 events for patients on placebo. There was no obvious recurring pattern seen for the high-grade AEs as reported and none were considered causally related to study medication.

There was overall a higher incidence of SAEs in the darolutamide arm compared to placebo arm (24.8% vs 20% respectively). Most of the SAEs individually occurred at low incidence. The SOC with the highest incidence of SAEs was cardiac disease, (5.3% darolutamide vs 3.2% placebo).

The incidence of deaths was lower in the darolutamide arm 8.3% compared to placebo arm 10.5% in the pivotal study in nmCRPC. The most common cause of death was prostate cancer followed by 'other specify' and 'cardiovascular disease'. On reviewing the MedDRA PT for the category 'Other, specify', there were potentially 2 additional deaths within cardiovascular disease category for darolutamide arm (heart injury and angina pectoris) and one additional death in the placebo arm (cardiac arrest). Despite comparable rates of death due to cardiovascular disease between arms, 1.9% in darolutamide arm vs 2.0% in the placebo arm, cardiovascular disease accounted for 22.8% of all the deaths in the darolutamide arm vs only 19% of all the deaths in the placebo arm. Heart failure and ischemic heart disease have been included as ADRs in the SmPC section 4.8.

Grade 5 TEAEs occurred in 3.9% of patients in the darolutamide arm and in 3.2% of patients in the placebo arm. It is acknowledged that numbers are low, however in the darolutamide arm there were two Grade 5 events (0.2%) of pulmonary embolism with no corresponding events in the placebo arm which is not negligible considering these patients were non metastatic at study entry.

Based on available laboratory data, a causal role of darolutamide in neutrophil count decreased, in aspartate aminotransferase (AST) increased and in blood bilirubin increased has been suggested. Adequate information has been included in this regard in section 4.8 of the SmPC.

Based on the available safety data, it is considered that darolutamide has no or negligible influence on the ability to drive and use machines (see SmPC section 4.7).

The highest dose of darolutamide studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose. Considering the saturable absorption (see section 5.2) and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity. In the event of intake of a higher than recommended dose, treatment with darolutamide can be continued with the next dose as scheduled. There is no specific antidote for darolutamide and symptoms of overdose are not established (see SmPC section 4.9).

In relation to special population, patients with severe renal function at baseline were poorly represented. Only one patient was included in darolutamide arm of study 17712. Given the 2.5-fold increase in exposure in patients with severe renal function, those patients should be closely monitored for adverse reactions (see SmPC

section 4.4). Furthermore, the use in patients with severe renal impairment has been included as missing information in the RMP.

In the nmCRPC study 17712, no meaningful differences were observed between the hepatic function groups or treatment arms in the overall incidence of TEAEs, or in the incidence of TEAEs with worst grade of 3, 4 or 5. However, in the mCRPC pool Grade 5 TEAEs and SAEs occurred more commonly in patients with mildly impaired hepatic function than in patients with normal liver function. Patients with severe hepatic impairment were not represented. No patients were included in the nmCRPC study 17712 or in the mCRPC pool. Overall, the data on patients with baseline hepatic impairment is considered limited (see SmPC section 4.4). ADRs resulting from increased exposure in patients with severe hepatic impairment will be closely monitored as reflected in the RMP under important potential risk.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC is a contraindication (see SmPC section 4.3).

Nubeqa contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product (see SmPC section 4.4).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Adequate risk minimisation measures have been put in place to manage adverse drug reactions. If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction (see SmPC section 4.8), dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily. Dose reduction below 300 mg twice daily is not recommended, because efficacy has not been established (see SmPC section 4.2).

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product as well as to monitor the effectiveness of the risk minimisation measures. As part of the routine pharmacovigilance activity, targeted follow-up questionnaires will be implemented to obtain structured information on reported suspected adverse reactions in patients with history of hepatic impairment, history of renal impairment and patients with cardiac disorders.

2.6.2. Conclusions on the clinical safety

Overall, darolutamide appears to be well tolerated in study ARAMIS 17712 with a low overall incidence of TEAEs. As with other androgen receptor antagonists in this class, darolutamide is associated with increased incidence of fatigue, rash, musculoskeletal pain and pain in extremity. However, these appeared manageable with most events being of grade 1 or 2 in severity. Darolutamide was also associated with a higher incidence of neutropenia, increased bilirubin and increased AST levels. Based on clinical data available there was no incremental risk with the addition of darolutamide to ADT for AEs such as fracture, fall, seizure, hypertension, weight decrease, mental impairment, diabetes and hyperglycaemia, cerebrovascular disorders, vasodilatation and flushing, depressed mood disorders, and breast disorders/gynecomastia.

Some of the reported events (cardiac disorders, seizures, flushing or hot flushes, hypertension, gynecomastia, thromboembolic events [venous, arterial and ischemic CNS], neutrophil count decreased/ neutropenia and pneumonitis) will be closely monitored in PSUR.

2.7. Risk Management Plan

Safety concerns

Table 43: Summary of safety concerns

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

ADR = Adverse drug reaction; CV = Cardiovascular

Pharmacovigilance plan

Table 44: Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
		Missing information:	Draft Report	End 2021

Table 44: Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Studies to assess the carcinogenic potential in mice Planned	The pilot study will assess general tolerability based on body weight, clinical pathology and necropsy data. In addition, toxicokinetics will be evaluated for the dose levels tested. In the main study, tumour incidence will be assessed in darolutamide-treated CByB6F1 Tg(HRAS)2Jic Mice compared to a vehicle control group.	Carcinogenicity potential	Final Report	Mid 2022

Risk minimisation measures

Table 45: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: **ADRs resulting from increased exposure in patients with severe hepatic impairment**	Routine risk communication for informed decision-making • SPC sections 4.2; 4.4; 4.8; 5.2 Other routine risk minimisation measures beyond the Product Information • Nubeqa is a prescription-only medicine Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Updates on important potential risks will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. • Follow-up questionnaire in patients with history of hepatic impairment
Important potential risk: **Cardiovascular events in patients with significant CV history**	Routine risk communication for informed decision-making • SPC section 4.2; 4.4; 5.1 Other routine risk minimisation measures beyond the Product Information • Nubeqa is a prescription-only medicine Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Updates on important potential risks will be provided in each PBRER/PSUR, if new safety relevant information is

Table 45: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		received during the period of the report. • Follow up questionnaire on cardiac disorders
Missing information: **Use in patients with severe renal impairment**	Routine risk communication for informed decision-making • SPC section 4.2; 4.4; 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk Other routine risk minimisation measures beyond the Product Information • Nubeqa® is a prescription-only medicine Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Updates on missing information will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. • Follow up questionnaire in patients with history of renal impairment
Missing information: **Carcinogenicity potential**	Routine risk communication for informed decision-making • SPC section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk None proposed Other routine risk minimisation measures beyond the Product Information • Nubeqa is a prescription-only medicine Additional risk minimisation measures None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Updates on missing information will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Additional pharmacovigilance activities: • Non-clinical study to assess the carcinogenic potential in mice (Category III)

ADR: Adverse Drug Reaction; CV: Cardiovascular; PBRER: Periodic Benefit-Risk Evaluation Report; PSUR: Periodic Safety Update Report; SPC: Summary of Product Characteristics

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 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 30 July 2019. 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 darolutamide 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 darolutamide 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. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nubeqa (darolutamide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

The application is for Nubeqa in the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease (prostate specific antigen doubling time (PSADT) of ≤ 10 months and PSA levels ≥ 2 ng/mL). Medical castration with gonadotropin releasing hormone analogue (GnRHa) should be continued during treatment in patients not surgically castrated.

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. Signs of resistance to androgen deprivation therapy (ADT) include rising PSA level, which represents chemical progression before radiologically detectable metastases. Non-metastatic CRPC patients with a PSADT of ≤10 months are at the highest risk for developing imminent metastatic disease and prostate cancer-specific death.

The delay of metastases and the associated morbidity for as long as possible is the goal of therapy for men with nmCRPC.

3.1.2. Available therapies and unmet medical need

Prior to 2018, there were no approved medicines for this indication and the management was conservative with serial PSA monitoring to assess the doubling time. Since then two AR antagonists, enzalutamide and apalutamide, have been approved for the treatment of non-metastatic castrate resistant prostate cancer at high risk of developing metastasis.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a randomized, double-blind, placebo-controlled, multi-centre Phase 3 trial to evaluate darolutamide vs placebo administered concurrently with ADT in patients with nmCRPC who are at high risk for developing metastases (Study ARAMIS, 17712). A total of 1509 patients were randomly assigned in a 2:1 ratio to one of the following treatment arms: darolutamide (955 patients) or placebo (554 patients).

3.2. Favourable effects

At the time of data cut off, 3rd September 2018, efficacy results from the pivotal ARAMIS study in the target population included the main analysis planned for MFS (BIRC assessed) and the first interim analysis for OS.

At the time of the primary analysis, 23.1% patients in the darolutamide arm versus 39% in the placebo arm presented a MFS event. The results demonstrated a statistically significant improvement in MFS in favour of darolutamide (HR 0.413 (95% CI: [0.341; 0.500]) with a p-value of <0.000001. The median MFS (95% CI) was 40.37 months (95% CI: 34.33, NE) in the darolutamide group versus 18.43 months (95% CI: 15.51,

22.34) in the placebo group (Δ 21.94 months). These results are supported by several sensitivity analyses as well as by subgroups analyses.

While still immature, the secondary endpoints showed consistency with primary efficacy outcomes. Only 136 out of a planned 240 OS events had occurred at an interim analysis. The HR was 0.706 95% CI [0.501; 0.994] and the median was not reached in either treatment arm. 8.2% versus 10.5% events had occurred in the darolutamide and placebo arm respectively. There was a positive trend for overall survival and the initial results presented for time to pain progression, initiation of first cytotoxic chemotherapy and first symptomatic skeletal event all favoured darolutamide.

The additional endpoints for example PFS, PSA progression and response, time to invasive procedure and the measures used to assess ECOG performance status deterioration and QoL currently favour darolutamide.

Specifically, PFS which was considered an additional endpoint demonstrated that 26.7% in the darolutamide arm vs 46.6% in the placebo arm experienced events. The median was 36.83 months for darolutamide and 14.82 months in the placebo arm with HR 0.38, 95%CI [0.319; 0.454] $p < 0.000001$.

3.3. Uncertainties and limitations about favourable effects

The data presented for the secondary and additional endpoints are still premature and reflect interim analyses only. The efficacy of darolutamide should be further investigated to confirm the positive trend observed. The final CSR of study ARAMIS is expected by 30 June 2020 (see Annex II condition).

ECOG performance status at baseline were 0 or 1. Thus efficacy of darolutamide in patients with ECOG > 1 is unknown (see SmPC section 5.1).

3.4. Unfavourable effects

The safety data of darolutamide (600 mg [2 tablets of 300 mg] b.i.d.) in the proposed indication are mainly based on the ARAMIS study. A total of 1508 patients received either darolutamide (N=954) or placebo (N=554) concurrently with ADT. Supportive safety data were derived from pooled analysis of Phase 1 and 2 studies in metastatic castration-resistant prostate cancer (mCRPC) patients (N=173).

Overall the incidence of individual TEAEs was low, with the only TEAE with incidence >10% in both treatment arms being fatigue which was reported in 12.1% and 8.7% of subjects in the darolutamide and placebo arms respectively in study ARAMIS.

In study ARAMIS the most common TEAEs included fatigue (12.1% vs 8.7%), diarrhoea (6.9% vs 5.6%), hypertension (6.6 vs 5.2%), pain in extremity (5.8% vs 3.2%), anaemia (5.6% vs. 4.5%), hot flush (5.2% vs. 4.2%), oedema peripheral (4.1% vs. 3.1%), pollakiuria (4.0% vs. 2.9%), headache (3.9% vs. 2.5%), musculoskeletal pain (3.9% vs. 2.0%), dizziness (3.7% vs. 2.5%), weight decreased (3.6% vs. 2.2%), cough (3.0% vs. 2.0%), rash (2.9% vs. 0.9%), influenza (2.8% vs. 1.6%), upper respiratory tract infection (2.6% vs. 1.6%) and pyrexia (2.0% vs. 0.9%).

Within the analysis of adverse events of special interest, there is discernible imbalance for darolutamide compared to placebo for cardiac arrhythmias (6.71% vs. 3.97%), coronary artery disorders (3.25% vs. 2.53%), and heart failures (1.89% vs. 0.90%) respectively. The SOC with the highest incidence of SAEs was also cardiac disease (5.3% darolutamide vs 3.2% placebo). Of note, among Grade 5 TEAEs two sudden death and two cardiac arrest were reported in the darolutamide arm. Even when the analysis is performed taking

background cardiac history into account, the incidence of CV AEs in patients without prior cardiac history remains higher in the darolutamide arm.

The safety of darolutamide treatment is considered unknown for patients experiencing the following within 6 months before treatment: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association Class III or IV (see SmPC sections 4.4 and 5.1). Considering the overall incidence of TEAEs in the SOC cardiac disorders was higher in the darolutamide arm compared to placebo arm, cardiovascular events in patients with significant cardiovascular history will be closely monitored as reflected in the RMP (important potential risk).

3.5. Uncertainties and limitations about unfavourable effects

Whilst overall there was no increased incidence of hypertension observed with darolutamide treatment, some of the hypertension events which occurred were significant and warrant further consideration. There was a higher incidence of Grade 3 hypertension compared to placebo. Hypertension will be closely monitored in PSUR.

The available data in patients with moderate hepatic impairment or severe renal impairment are limited and darolutamide has not been studied in patients with severe hepatic impairment (see SmPC sections 4.2 and 4.4). As exposure might be increased those patients will be closely monitored for adverse reactions (see SmPC and RMP). In addition, adequate measures to obtain structured information on reported suspected adverse reactions in patients with history of hepatic or renal impairment will be put in place as part of the routine pharmacovigilance activity (see RMP).

ECOG performance status at baseline were 0 or 1. Thus safety of darolutamide in patients with ECOG > 1 is unknown (see SmPC section 5.1).

3.6. Effects Table

Table 44: Effects Table for darolutamide in the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease (data cut-off 3 September 2018)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Metastasis Free Survival (MFS)	Primary endpoint Defined as time between randomisation and evidence of metastasis or death from any cause, whichever occurs first.	Median month (95% CI)	40.37 months (34.33 – NR)	18.43 months (15.51 – 22.34)	clinically meaningful difference of 21.94 months in favour of darolutamide. HR of 0.413 (95% CI: [0.341; 0.500]; p<0.000001)	Efficacy section of AR
Overall Survival (OS)	Secondary endpoint Defined as time from randomisation to date of death from any cause.	Median month (95% CI)	NR (44.45 – NR)	NR (NR-NR)	HR of 0.706 95% CI [0.501;0.994]. The median was not reached in either treatment arm. 8.2% versus 10.5% events.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Time to pain progression	Secondary endpoint Defined as time from randomisation to pain progression (an increase of ≥ 2 points from baseline (day 1 score) in question 3 of BPI-SF (related to the worst pain in the last 24 hours) taken as a 7-day average, or initiation of short or long-acting opioids for pain, whichever comes first)	Median month (95% CI)	40.31 (33.21 – 41.2)	25.36 (19.09 – 29.63)	Time to pain progression translated as a difference of 14.95 months in favour of darolutamide. 26.3% and 32.1% events. HR 0.647 95% [CI 0.533; 0.785] p= 0.000008	
Time to initiation of first cytotoxic agent	Secondary endpoint Defined as time from randomisation to initiation of the first cytotoxic chemotherapy	Median month (95% CI)	NR (NR – NR)	38.21 (35.55 – 41.89)	HR 0.433 95% [CI 0.314; 0.595] p=0.000001 7.6% v 14.3% events. Initial results show longer time to initiation of first cytotoxic chemotherapy for darolutamide	
Time to first symptomatic skeletal event (SSE)	Secondary endpoint. Defined as time from randomisation to the first occurrence of SSE (occurrence of any of the following: external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumour related orthopaedic surgical intervention)	Median month (95% CI)	NR (NR – NR)	NR (NR – NR)	HR 0.428 95% [CI 0.218; 0.842] p = 0.11. 1.7% v 3.2% events. Too low number of events but trending positive.	
Progression Free Survival (PFS)	Additional endpoint. Defined as time between randomisation and evidence of any radiographic disease progression, including new pathologic lymph nodes identified above or below the aortic bifurcation or death from any cause, whichever occurs first.	Median months (95% CI)	36.83 (32.92 – NR)	14.82 (11.83 – 18.43)	HR 0.38 95% [CI 0.319; 0.454] p < 0.000001. 26.7% v 46.6% events. PFS favours darolutamide.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
TEAEs	TEAEs regardless of causality	%	83.2	76.9		Safety section of AR
Grade 3-4 TEAEs	Grade 3-4 TEAEs regardless of causality	%	24.7	19.5		
Serious TEAEs	Serious TEAEs regardless of causality	%	24.8	20.0		
Deaths	Number of deaths related to TEAEs regardless of causality	%	3.9	3.2		
Fatigue	All Grade Grade 3-4	%	15.8 0.6	11.4 1.1		
Rash	All grade Grade 3-4	%	2.9 0.1	0.9 0		
Cardiac disorders	All grade	%	11.8	7.4		
Neutropenia	All grade Grade 3-4	%	19.6 3.5	9.4 0.5		

Abbreviations: NR: Not reached.
Notes: Abbreviations: AE (adverse event); AEOSI (adverse event of special interest); AR (assessment report); TEAE (treatment emergent adverse event)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Darolutamide demonstrated a significant improvement in metastasis free survival in patients with castrate resistant non metastatic prostate cancer with a PSA doubling time of ≤ 10 months and PSA levels ≥ 2 ng/mL. The improvement translated into a difference of 21.94 months.

The data presented for the secondary and additional endpoints are still premature and reflect interim analyses only. However, the results for overall survival shows a positive trend for darolutamide. PFS as an additional endpoint is favouring darolutamide which is reassuring. Further analysis will be required to ensure that this positive trend is maintained in favour of darolutamide and the final CSR of study ARAMIS will be submitted by 30 June 2020 (PAES).

Early results from secondary and additional endpoints evaluating patient's symptoms (pain, local symptoms) were positive. Prolonging the time to pain progression and time to treatment for first symptomatic skeletal events while also delaying additional treatment provide further support to the primary endpoint, especially given that the initial diagnosis of metastasis may not be symptomatic for the patient or require further treatment immediately. This is important given that men who are initially diagnosed as castrate resistant without metastasis are generally well and even once metastasis is diagnosed, can remain asymptomatic. It may take months even years to become significantly affected by their disease clinically.

The safety profile of darolutamide is considered well characterized at this stage and a number of adverse events will be closely monitored in PSUR: cardiac disorders, seizures, flushing or hot flushes, hypertension, gynecomastia, thromboembolic events [venous, arterial and ischemic CNS], neutrophil count decreased/ neutropenia and pneumonitis. As with other novel androgen receptor antagonists in this class, darolutamide has demonstrated increased incidence of rash, fatigue and musculoskeletal pain. However, these are predominantly lower grade AEs and generally tolerable.

In addition, adequate routine pharmacovigilance and risk minimisation measures are in place to manage the risks associated with Nubeqa.

3.7.2. Balance of benefits and risks

Darolutamide has shown a statistically significant improvement in metastasis free survival compared to placebo with a favourable safety profile in patients with castrate resistant non metastatic prostate cancer who are at high risk of developing metastatic disease. Although not yet mature, the interim analyses of the secondary endpoints support the primary analysis. Overall, the efficacy results are considered clinically meaningful.

From a safety perspective, the overall incidence of adverse events is low and darolutamide appears to be relatively well tolerated.

The main uncertainty is related to the immaturity of the OS results presented. However, the effect shown in delaying the development of metastasis overcome this uncertainty and this new treatment represents a valuable option for patients with nmCRPC who are at high risk of developing metastatic disease. Therefore, the B/R balance is considered positive.

The final CSR providing updated efficacy data on OS and other secondary endpoints will be submitted by 30 June 2020 (PAES).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Nubeqa in the treatment of adult men with non-metastatic castration-resistant prostate cancer (NM-CRPC) who are at high risk of developing metastatic disease is positive.

4. Recommendations

Outcome

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

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

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
PAES: In order to further investigate the efficacy of darolutamide in adult men with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease, the MAH should submit the final study report, including updated OS results, from study ARAMIS 17712.	30 June 2020

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

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