EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2023
EMA/80060/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NUBEQA

International non-proprietary name: darolutamide

Procedure No. EMEA/H/C/004790/II/0009

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

A	Value cannot be estimated
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ARI	Androgen receptor inhibitor
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BID	Twice daily
BM	Biomarker(s)
BPI-SF	Brief pain inventory – short form
BS	Bone scan
CBF	Cerebral blood flow
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CO	Cross-over
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYTOC	Cytotoxic chemotherapy
CYP	Cytochrome P450
Daro	Darolutamide
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
DLT	Dose-limiting toxicity

DRS-E Disease-related emotional symptoms

DRS-P Disease-related physical symptoms

EAIR Exposure-adjusted incidence rates

EBRT External beam radiation therapy

ECG Electrocardiogram

ECOG (PS) Eastern Cooperative Oncology Group (performance status)

eGFR Estimated glomerular filtration rate

EMA European Medicines Agency (EU)

EPAR European Public Assessment Report

ePRO Electronic patient reported outcome

EOT End of treatment

ESMO European Society for Medical Oncology

EudraCT European Clinical Trials Database

FACT- Functional assessment of cancer therapy

FPSI-17 Functional assessment of cancer therapy / Prostate cancer symptom index 17 item questionnaire

FACT-P Functional assessment of cancer therapy / Prostate

FAS Full analysis set

FDA Food and Drug Administration (US)

DRS-P FPSI–17 disease-related symptoms – physical

FWB Function and well-being

GCP Good Clinical Practice

GI Gastrointestinal

GLP Good Laboratory Practices

GnRH Gonadotropin-releasing hormone

HIV Human immunodeficiency virus

HLGT High level group term

HLT High level term

HR Hazard ratio

HRQoL Health-related Quality of life

HSPC Hormone-sensitive prostate cancer

ICH International Council for Harmonization

INR International normalized ratio

ITT Intent-to-treat

IV Intravenous

IxRS Interactive voice/web response system

LHRH Luteinizing hormone-releasing hormone

LPLV Last patient last visit

KM Kaplan-Meier

Max Maximum

MedDRA Medical Dictionary for Regulatory Activities

mCRPC Metastatic castration-resistant prostate cancer

mCSPC Metastatic castration-sensitive prostate cancer

MFS Metastasis-free survival

mHSPC Metastatic hormone-sensitive prostate cancer

MID Minimally important difference

Min Minimum

MLG MedDRA labeling grouping

MTD Maximum tolerated dose

MRI Magnetic resonance imaging

n Number of patients with event

N Total number of patients

NA Not applicable / Not available

NCA Non-compartmental analysis

NCCN National Comprehensive Cancer Network

NCI National Cancer Institute

FPSI-17 National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy - Prostate Symptom Index

NCI-ODWG National Cancer Institute Organ Dysfunction Working Group

NE Not evaluable

nmCRPC Non-metastatic castration-resistant prostate cancer

NYHA New York Heart Association

OL Open-label

OS Overall survival

PBRER Periodic Benefit-Risk Evaluation Report

PC Prostate cancer

PCWG3 Prostate Cancer Clinical Trials Working Group 3

PD Pharmacodynamics

PFS Progression-free survival

PK Pharmacokinetic(s)

Pla Placebo

PMDA Pharmaceuticals and Medical Devices Agency (Japan)

popPD Population pharmacodynamics

PP Pain progression

PRO Patient reported outcome

PS Performance status

PSA Prostate-specific antigen

PSADT Prostate-specific antigen doubling time

PT Preferred term

PY Patient year

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 corrected for heart rate

QTcF QT interval corrected for heart rate using the Fridericia's formula

RECIST v1.1 Response Evaluation Criteria in Solid Tumors version 1.1

ROW Rest of the world

rPFS Radiographic progression-free survival

SAE Serious adverse event

SAF Safety population

SAP Statistical analysis plan

SCE Summary of Clinical Efficacy

SOC Standard of care

SSE Symptomatic skeletal event

SSE-FS Symptomatic skeletal event-free survival

StD Standard deviation

TEAE Treatment-emergent adverse event

TSE Treatment side effects

TURP Transurethral resection of the prostate

UK United Kingdom

ULN Upper limit of normal

US(A) United States of America

USPI United States Prescribing Information

WBC White blood cell

WHO-DD World Health Organization Drug Dictionary

WPS Worst pain subscale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 4 March 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel, based on final results from Study 17777 (ARASENS); this is a randomized, double-blind, placebo-controlled Phase 3 study designed to demonstrate the superiority of darolutamide in combination with docetaxel over placebo in combination with docetaxel in OS in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.5, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. As part of the application, the MAH is also requesting one additional year of market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

MAH request for additional market protection

Initially the Market Authorization Holder (MAH) requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The request was withdrawn during the procedure.

Scientific advice

The MAH received Scientific advice (SA) from the CHMP on 24 September 2015 (EMEA/H/SA/2639/2/2015/II). The Scientific advice pertained to clinical aspects of the dossier. SA was provided on the use of androgen deprivation therapy (ADT) (i.e. orchiectomy, luteinizing hormone-

releasing hormone (LHRH) agonists or antagonists) based on investigator's choice, which was considered acceptable by the CHMP; the use of docetaxel as backbone treatment; the proposed stratification factors (i.e. extent of disease and the level of alkaline phosphatase) as well as the primary endpoint (overall survival) and the statistical design and secondary endpoints. Some other questions were raised to the CHMP.

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: Blanca Garcia-Ochoa

Timetable	Actual dates
Submission date	4 March 2022
Start of procedure:	26 March 2022
CHMP Rapporteur Assessment Report	25 May 2022
PRAC Rapporteur Assessment Report	31 May 2022
PRAC members comments	1 June 2022
CHMP Co-Rapporteur Critique	8 June 2022
Updated PRAC Rapporteur Assessment Report	2 June 2022
PRAC Outcome	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2022
Request for supplementary information (RSI)	23 June 2022
CHMP Rapporteur Assessment Report	17 August 2022
PRAC members comments	24 August 2022
PRAC Outcome	1 September 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur Assessment Report	9 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	15 November 2022
PRAC Rapporteur Assessment Report	18 November 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	24 November 2022
PRAC Outcome	01 December 2022
CHMP members comments	05 December 2022
Updated CHMP Rapporteur Assessment Report	08 December 2022
Request for Supplementary Information	15 December 2022
PRAC Rapporteur Assessment Report	03 January 2023
PRAC members comments	04 January 2023

Timetable	Actual dates
Updated PRAC Rapporteur Assessment Report	05 January 2023
CHMP Rapporteur Assessment Report	11 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur Assessment Report	19 January 2023
CHMP opinion	26 January 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed the therapeutic indication

The applied indication for Nubeqa was for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

The recommended indication is: NUBEQA is indicated for the treatment of adult men with metastatic hormone sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy (see section 5.1).

Epidemiology

Prostate cancer is the second most frequent cancer diagnosed in men, and the fifth leading cause of death in the world. Based on Global Cancer Observatory (GLOBOCAN) 2020 estimates, 1,414,259 new cases of prostate cancer were reported worldwide, with higher prevalence in developed countries (Sung et al. 2021). In Europe, the estimated number in 2020 of new prostate cancer cases was approximately 473,344, and the number of deaths was approximately 108,088 (Sung et al. 2021).

Clinical presentation, diagnosis and stage/prognosis

Metastatic HSPC is defined as metastatic prostate cancer in patients who have not yet received or are continuing to respond to anti-hormonal therapy. Depriving prostate cancer cells of androgen is the primary form of therapy since prostate cancer depends on androgen for growth and survival. Androgen deprivation therapy (ADT) is defined as surgical castration by bilateral orchiectomy or medical castration with LHRH agonist/antagonists. Metastatic HSPC can occur due to recurrence after initial local treatment with surgery and/or radiotherapy, or as de novo disease in patients whose first diagnosis of prostate cancer is metastatic disease (Lowrance et al. 2021).

Metastatic castration resistant prostate cancer is associated with a range of symptoms but is predominantly characterised by bone pain, fatigue, and urinary dysfunction. Metastasis is predominantly

localized in bones (90% of patients with metastatic castration-resistant prostate cancer), causing significant morbidity which requires medical interventions.

Although almost all men with mHSPC initially respond to ADT, most will progress to mCRPC within 1 to 3 years of their initial diagnosis (Wenzel et al. 2021).

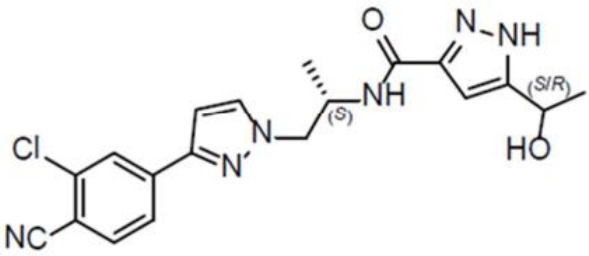
Management

The treatment and management of patients with mHSPC has evolved over recent years with several new treatment options. Historically, for decades ADT, achieved by surgical or medical castration, was the standard of care (SOC) for mHSPC. Nowadays, ADT in combination with one of the following is currently approved in the EU for the treatment of mHSPC: abiraterone, a CYP17 inhibitor (with prednisone or prednisolone), apalutamide, an androgen receptor inhibitor (ARI), or enzalutamide, another ARI. In the EU, docetaxel in combination with ADT, with or without prednisone or prednisolone, is also approved for the treatment of mHSPC. (C Parker et al. Ann Oncol 2020)

2.1.2. About the product

Darolutamide is a structurally distinct non-steroidal ARI that binds with a high affinity and selectivity to the AR, thus inhibiting androgen binding, AR nuclear translocation and AR mediated transcription, thus preventing transcription of oncologic genes necessary for cancer growth and survival.

Chemical structure of darolutamide



Darolutamide (Nubeqa) was first approved in the EU on 27 March 2020 for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.

The recommended dose is 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg. The proposed dose for the current indication is the same. Darolutamide should be continued until disease progression or unacceptable toxicity. mHSPC patients should start darolutamide in combination with docetaxel.The first of 6 cycles of docetaxel should be administered within 6 weeks after the start of darolutamide treatment. Treatment with darolutamide should be continued until disease progression or unaccepatble toxicity even if a cycle of docetaxel is delayed, interrupted, or discontinued.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The pivotal study to support efficacy and safety of darolutamide for the treatment in the mHSPC population is the randomized, double-blind, placebo-controlled Phase 3 Study 17777 (ARASENS). Study 17777 was designed to demonstrate the superiority of darolutamide in combination with docetaxel over placebo in combination with docetaxel in overall survival (OS). The study randomized 1306 patients in

a 1:1 ratio to receive 6 cycles of docetaxel and either darolutamide + docetaxel + ADT or matching placebo+docetaxel concurrently with ADT until disease progression.

The MAH sought Scientific Advice at the CHMP on the design of study 17777, the pivotal trial for this application (EMEA/H/SA/2639/2/2015/II) (See section 1). The MAH mostly followed the recommendations of the CHMP scientific advice.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

2.2.1. Introduction

New non-clinical studies as well as environmental studies have been submitted in support to this procedure. The non-clinical studies are oncology studies conducted in transgenic mice submitted and discussed under Variation EMEA/H/C/004790/II/0012. The submitted study on the environmental risk was an update of the study submitted in 2019.

2.2.2. Pharmacology

2.2.3. Toxicology

Carcinogenicity

The carcinogenic potential of darolutamide was evaluated in a 6-month study in TgRAS transgenic mice. Seven -day and 4-week studies were also conducted to select the appropriate dosing regimen for the 6-month study.

The chosen maximum tolerated dose was 500 mg/kg twice daily.

2.2.4. Ecotoxicity/environmental risk assessment

Substance: darolutamide			
CAS-number: 1297538-32-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.41	Not potential PBT
PBT assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	Log K_{ow}	2.41	Not B

Persistence	DT50	Darolutamide: up to 542.37 d (total system,12°C) M-1 (keto-darolutamide): up to 2139.74 d (total system, 12°C)			vP
Toxicity	NOEC (fish)	NOEC = 28 µg/L			Not T
PBT-statement	The compound is not considered as PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$	1.74	mg/L			>0.01 threshold: Yes
Other concerns	Endocrine active substance				Yes
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$Kf_{oc\ soil}$ = 186; 910; 1877 $Kf_{oc\ sludge}$ = 244; 452			
Water solubility	OECD 105	12.9 mg/L (25ºC, pH 6)			
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	$DT_{50,\ water}$ = < 1 d $DT_{50,\ sediment}$ = 129.55 d - 289.76 d $DT_{50,\ total\ system}$ = 129.55 d - 289.76 d Transformation product > 10%: M-1 (keto-darolutamide) DT50, total system = 2139.74 d Sediment-shifting: 67%/ 33.6% (day 15)			sandy clay and sand, 12°C sediment 1 and total system: SFO kinetic; sediment 2 and total system HS kinetic
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	⩾8037	µg/L	*Desmodesmus subspicatus*
Daphnia sp. Reproduction Test	OECD 211	NOEC	⩾1137	µg/L	*Daphnia magna*
Fish, Short Term Reproduction Screen	OECD 229	NOEC	⩾119	µg/L	*Pimephales promelas*
Fish, Full Life-Cycle Toxicity Test	OECD 240 adapted	NOEC	28	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	⩾12900	µg/L	Maximum water solubility
Phase IIb Studies					
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC	128.16	mg/kg	Sediment dry weight, 10% Corg

Regarding the environmental risk, the data submitted provide the results of 2 new studies which aim to assess the endocrine disrupting (ED) potential of darolutamide.

On the basis of these study results, it appears that darolutamide poses a risk to aquatic organisms in surface waters. This result leads the manufacturer to calculate a Refined PECsw (based on a refined Fpen) which no longer showed any risk for aquatic organisms in surface waters.

2.2.5. Discussion on non-clinical aspects

The carcinogenic potential of darolutamide was evaluated in a 6-month study in TgRAS transgenic mice presented in Variation EMEA/H/C/004790/II/0012. The study was well constructed about number of mice, positive and negative controls. The chosen maximum tolerated dose was 1000 mg/kg/day. This is a dose which did not show any toxicity in transgenic mice. Beyond this dose, the appearance of an exposure plateau justified the choice of this maximum dose. The results of this study did not demonstrate an increase in tumor development in mice treated with darolutamide versus untreated mice. However, studies in transgenic mice alone and the maximum dose used do not offer sufficient safety margins to rule out the risk of second primary cancers in humans.

Since darolutamide unlike other second-generation anti-androgens did not produce pre-neoplastic lesion in repeated toxicity studies and in order to reduce the use of animals, the need for 2-year studies in rats, was waived.

2.2.6. Conclusion on the non-clinical aspects

The 6-month study in transgenic mice did not show significantly higher tumor occurrence in treated mice compared to negative controls. However, this study alone does not rule out the risk of a second primary cancer in humans, especially since the safety margins are low. The non-discarded risk of development of a second primary cancer in humans has been added to the SmPC.

Darolutamide was found to be very persistent and not readily biodegradable but without toxicity to aquatic organisms.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

Bayer study no Study name (Orion study no) Study report no/ Region	Study design	Treatment and dose	Main objectives	Study population	Treated patients as of 25 OCT 2021
Phase 3 pivotal study in mHSPC – PRIMARY COMPLETION					
17777 **ARASENS** Primary completion North America, Asia Pacific, ROW	Randomized 1:1, double-blind placebo-controlled	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg, or placebo. In combination with 6 cycles of docetaxel at 75 mg/m^2 as an IV infusion every 21 days Concurrently with ADT	Efficacy and safety compared with placebo, in combination with docetaxel	Patients with mHSPC	darolutamide+ docetaxel **652** placebo+docetaxel **650** 424 patients ongoing with treatment (299 darolutamide+ docetaxel arm; 125 placebo+ docetaxel arm) as of 25 OCT 2021

2.3.2. Pharmacokinetics

Darolutamide pharmacokinetic (PK) in mHSPC patients has been investigated in Study 17777 ARASENS using non-compartmental analysis (NCA) and population PK modelling and simulation techniques (study number CPMX50017 / report R-13408, report date 10 January 2022). This pivotal study was a randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of 600 mg (bis in die) BID oral darolutamide in combination with docetaxel (75 mg/m^2 Day 1 as 1 h intravenous [IV] infusion every 21 days) in mHSPC patients for six treatment cycles.

In addition, the PK has been investigated in a subgroup of Chinese patients who were randomized to the darolutamide+docetaxel arm. Moreover, exposure-response analysis was provided.

Clinical pharmacology data in mHSPC patients were compared, where applicable, with the previously submitted data in nmCRPC patients from a Phase 3 Study 17712 (ARAMIS).

2.3.2.1. Methods

2.3.2.1.1. Bioanalytical methods

- Darolutamide

In study 17777, bioanalysis of darolutamide, the two diastereomers, (S,R)-darolutamide and (S,S)-darolutamide, and its metabolite keto-darolutamide in human plasma (K2EDTA) was performed utilizing quantitative high performance LC-MS/MS assay. All Samples were stored at nominal temperature of -20°C and analysed within at most 728 days after sampling. The stability data indicated that the analyte(s) were stable for this time period. A summary of the calibration range, precision and accuracy is provided in **Table *1***. The lower limit of quantification (LLOQ) values for (S,R)-darolutamide, (S,S)-darolutamide, keto-darolutamide and docetaxel were 4.87 µg/L, 5.13 µg/L, 10 µg/L and 1 µg/L respectively.

Table 1: Brief summary of working range and precision and accuracy of the bioanalytical method darolutamide in human plasma

	(*S*,*R*)-darolutamide (BAY 1896951)	(*S*,*S*)-darolutamide (BAY 1896952)	Keto-darolutamide (BAY 1896953)
Calibration range (ng/mL) of runs 1 to 10 [a]	4.94 to 4940	5.06 to5060	10.0 to 10000
Calibration range (ng/mL) of runs 11 to 52 [a]	4.87 to 4870	5.13 to 5130	10.0 to 10000
Mean inter-assay accuracy range (%) of back-calculated concentrations of runs 1 to 10 (except LLOQ) in calibrators	95.5 to 102.3	96.8 to 101.2	97.2 to 102.2
Mean inter-assay accuracy range (%) of back-calculated concentrations of runs 11 to 52 (except LLOQ) in calibrators	98.4 to 101.5	98.9 to 101.0	n.a. [b]
Mean inter-assay precision range (%) of runs 1 to 10 of back-calculated concentrations (except LLOQ) in calibrators	2.4 to 6.6	1.8 to 3.5	1.7 to 3.5
Mean inter-assay precision range (%) of runs 11 to 52 of back-calculated concentrations (except LLOQ) in calibrators	1.8 to 5.3	1.9 to 4.1	n.a [b]
Accuracy (%) of runs 1 to 10 (LLOQ)	103.0	101.0	102.0
Accuracy (%) of runs 11 to 52 (LLOQ)	100.6	100.4	n.a. [b]
Precision (%) of runs 1 to 10 (LLOQ)	3.0	1.8	1.6
Precision (%) of runs 11 to 52 (LLOQ)	2.6	1.9	n.a. [b]
Quality control range (ng/mL) of runs 1 to 10	14.8 to 19800	15.2 to 20200	30.0 to 40000
Quality control range (ng/mL) of runs 11 to 52	14.6 to 19480	15.4 to 20520	30.0 to 40000
Accuracy (%) of runs 1 to 10	100.2 to 103.7	100.0 to 103.3	100.6 to 102.1
Accuracy (%) of runs 11 to 52	99.9 to 101.8	100.3 to 102.0	n.a [b]
Precision (%) of runs 1 to 10	5.7 to 6.6	3.7 to 6.8	3.1 to 5.9
Precision (%) of runs 11 to 52	4.6 to 5.7	2.8 to 5.8	n.a. [b]

Abbreviations: LLOQ= Lower limit of quantification
[a]The calibration range is based on the diastereomeric ratio shown in this study:
for runs 1-10: 49.4% (BAY 1896951, R form), 50.6% (BAY 1896952, S-form)
for runs 11-52: 48.7% (BAY 1896951, R form), 51.3% (BAY 1896952, S-form).
[b] Identical range for BAY 1896953 throughout study, data for runs 1 to 52 for BAY 1896953 summarized and only shown once

- Docetaxel

In study 17777, quantitative analysis of docetaxel in plasma was performed utilizing liquid phase extraction followed by quantitative high performance LC-MS/MS detection, with quantitation being achieved by weighted linear regression using paclitaxel as the internal standard. All samples were stored at -20°C and -80°C and analysed within 1158 days after sampling. The stability data indicated that docetaxel was stable for this time period. A summary of the calibration range, precision and accuracy is provided in **Table *2***.

Table 2: Brief summary of working range and precision and accuracy of the bioanalytical method docetaxel in human plasma

Docetaxel	
Calibration standards mean inter-assay accuracy of back-calculated concentrations	97.00% to 103.00%
Calibration standards precision	≤ 6.13%
Accuracy at the lowest calibration standard (LLOQ)	99.40%
Precision at the lowest calibration standard (LLOQ)	5.29%
Concentration range of Quality control (QC) samples (µg/L)	15.0 to 3750
QC accuracy	91.20% to 98.00%
QC precision	5.81% to 7.22%

2.3.2.1.2. Pharmacokinetic analyses

The PK of darolutamide (i.e. the sum of the two diastereomers (S,S), and (S,R)-darolutamide), (S,S)-darolutamide, (S,R)-darolutamide, keto-darolutamide, and docetaxel were evaluated in study 17777 ARASENS.

PK data were analysed using NCA and population PK modelling. NCA evaluation was performed using WinNonlin Phoenix (Certara). Population PK modelling and simulation was performed using the nonlinear-mixed effects modelling approach with NONMEM software (ICON Development Solutions, version 7.4).

In the first 25 patients (safety/PK lead-in) PK samples were taken on day 1 pre-dose, and after 20 min, 1h, 1.5 h, 2 h, 3 h, 4 h, 6 h, and 8 h post-dose, as well as two additional samples at two later visits (one per visit). For those who received at least 1 cycle of docetaxel, $AUC_{(0-12)}$ (using the pre-dose plasma sample also as 12 hour sample), $AUC_{(0-8)}$, $AUC_{(0-tlast)}$, C_{max}, t_{max}, t_{last} were estimated for darolutamide, (S,S)-darolutamide, (S,R)-darolutamide, keto-darolutamide, and docetaxel. For docetaxel, $AUC_{(0-t\ last)}$, C_{max}, t_{max}, and t_{last} were estimated.

For all other patients, sparse PK sampling was done.

China PK substudy: At sites in China additional blood samples at visit 1 (days 1, 2 and 3), and day 15 for assessment of pharmacokinetics were drawn. Differences in study drug administration compared to the main study were (i) single dosing of study drug on day 1, (ii) study treatment holiday on day 2, and (iii) tart of regular twice-a-day dosing of study drug on day 3.

Absorption

The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC showed that peak plasma concentrations (C_{max}) of darolutamide following oral administration of 600 mg (2 tablets of 300 mg), were about 20 % lower compared to those observed in study 17712 ARAMIS in patients with nmCRPC (i.e. 3.84 mg/L [35.6 %CV] versus 4.79 mg/L [30.9 %CV]).

In study 17712 ARAMIS in patients with nmCRPC C_{max} were usually reached around 4 hours after administration.

Distribution

The apparent volume of distribution of darolutamide after intravenous administration is 119 L. The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC reveal an overall volume of distribution of 32.7 L (117 %CV) after oral administration of 600 mg BID of darolutamide.

Elimination

The clearance of darolutamide following intravenous administration was 116 mL/min (CV: 39.7%).

In study 17712 ARAMIS in patients with nmCRPC the effective half-life of darolutamide and keto-darolutamide in plasma of patients was approximately 20 hours. Of the two diastereomers comprising darolutamide, (S,R)-darolutamide had a shorter effective half-life of 9 hours compared to (S,S)-darolutamide with an effective half-life of 22 hours.

The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC revealed that the effective half-life of darolutamide, (S,R)-darolutamide, (S,S)-darolutamide, and

keto-darolutamide in plasma of patients were approximately 18.4 h (62 %CV), 10.9 h (76.2 %CV), 20.5 h (58.8 %CV), and 19 h (63.2 %CV), respectively.

Dose proportionality and time dependencies

No new information submitted.

2.3.2.2. Intra- and inter-individual variability

Variability was reported to be higher in study 17777 ARASENS in patients with mHSPC (**Table *8***) compared to study 17712 ARAMIS in patients with nmCRPC (**Table *11***).

2.3.2.3. Pharmacokinetics in target population

The PK in the pivotal study 17777 ARASENS was analysed using NCA and population PK modelling methods.

The PK parameters from NCA analysis and population PK analysis are listed in **Table *3***.

Table 3 Geometric mean (%CV) of darolutamide PK parameters from Study 17712 (population PK approach) and from Study 17777 (NCA approach and population PK approach)

	Study 17777 Pop PK (n=652)	Study 17777 NCA (n=11-12)	Study 17712 Pop PK (n=388)
C_{max}, mg/L	3.84 (35.6%)	4.33 (50%)	4.79 (30.9%)
tmax, h	3.33 (18.4%,1.35–4.59)	3.83 [0.00–8.13]	3.64 (4.4%, 2.72–3.92)
AUC(0–12), mg·h/L	38.2 (39.1%)	35.5 (75%)	52.8 (33.9%)
Effective $t_{1/2}$, h	18.4 (62.0%)	NA	19.6 (29.7%)

Abbreviations: AUC(0–12)=Area under the plasma concentration-time curve from time 0 to 12 hours post dose; Cmax=Maximum observed drug concentration; CV=Coefficient of variation; PK=Pharmacokinetic; tmax=Time to maximum observed drug concentration; t1/2=Half-life, NA=not available

Study 17777 ARASENS

Overall, 1305 patients were randomly assigned to receive darolutamide + docetaxel + Androgen deprivation therapy (ADT); (n = 651 patients) or placebo + docetaxel + ADT (n = 654 patients). At the time of the primary completion, 45.9% of the randomized patients in the darolutamide + docetaxel + ADT arm and 19.1% in the placebo + docetaxel + ADT arm were ongoing with study treatment.

All patients were required to receive treatment with ADT of the investigator's choice (luteinizing hormone Patients were randomly assigned in a 1:1 ratio to receive darolutamide or placebo at 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg. Randomization was stratified by extent of disease and alkaline phosphatase (ALP) levels. Docetaxel was administered after randomization, at a dose of 75 mg/m^2 as an IV infusion every 21 days for 6 cycles, and the first cycle was to be administered within 6 weeks after the start of study drug. Docetaxel could be administered in combination with prednisone/prednisolone at the discretion of the investigator. All patients were required to receive ADT of the investigator's choice (luteinizing hormone-releasing hormone [LHRH] agonist/antagonists or orchiectomy) as standard therapy starting ≤12 weeks before randomization.

NCA results for study 17777 ARASENS

Safety/PK lead-in phase

In total, PK data from 25 patients were evaluated during the safety/PK lead-in phase. Among those, 12 patients were randomized into the darolutamide + docetaxel arm.

The results from NCA evaluation showed a slight increase in exposure in the darolutamide + docetaxel arm compared with the placebo + docetaxel arm (**Table *4***) with the $AUC_{(0-tlast)}$ being 6% higher (2.10 vs. 1.98 mg*h/L) and C_{max} being 15% higher (1.93 vs. 1.68 mg/L) in the darolutamide + docetaxel arm (23 – 54 %CV docetaxel).

Table 4: Geometric mean (%CV) PK parameters of docetaxel after repeated administration of 600 mg darolutamide BID on the first day of docetaxel administration of 75 mg/m² (PKS– Safety/PK lead-in)

Parameter	Unit	Darolutamide+ docetaxel arm (n=12) [a]	Placebo+ docetaxel arm (n=13) [a]
$AUC(0–t_{last})$	µg·h/mL	2.10 (30%) [b]	1.99 (33%) [c]
C_{max}	µg/mL	1.93 (23%) [b]	1.68 (54%) [c]
t_{max} [a]	h	1.00 [0.33 – 1.50] [b]	0.967 [0.167 – 2.25] [c]
t_{last} [a]	h	7.85 [5.83 – 8.00]	7.92 [6.00 – 8.15]

Abbreviations: AUC=Area under the plasma concentration-time curve; BID=Twice daily; C_{max}=Maximum observed drug concentration; CV=Coefficient of variation; LLOQ=Lower limit of quantification; PK=Pharmacokinetic; PKS=Pharmacokinetic analysis set; t_{last}=Time of the last plasma concentration above LLOQ; t_{max}=Time to maximum observed drug concentration

a: Median [range]
b: n=11
c: n=12
Note: Units and values from the source data were transformed to µg/mL and rounded to 3 significant digits manually.

The PK parameters resulting from NCA evaluation of darolutamide, (S,R)-darolutamide, (S,S)-darolutamide, and keto-darolutamide are presented in **Table *5***. The corresponding concentration-time profiles are shown in Figure 1.

Table 5: Geometric mean (%CV) PK parameters of darolutamide, (S,S)-darolutamide, (S,R)-darolutamide, and keto-darolutamide after repeated administration of 600 mg darolutamide BID on the first day of docetaxel administration of 75 mg/m²(PKS– Safety/PK lead-in)

Parameter	Unit	Darolutamide (n=12)	(*S,R*)-darolutamide (n=12)	(*S,S*)-darolutamide (n=12)	Keto-darolutamide (n=12)
AUC(0–12) [a]	mg·h/L	35.5 (75%)	4.65 (48%)	30.3 (86%)	80.5 (70%)
AUC(0–8)	mg·h/L	24.4 (79%)	3.52 (50%)	20.6 (89%)	57.7 (73%)
$AUC(0–t_{last})$	mg·h/L	35.3 (71%)	4.49 (47%)	30.3 (81%)	82.1 (67%)
C_{max}	mg/L	4.33 (50%)	0.781 (37%)	3.51 (63%)	10.2 (57%)
t_{max} [b]	h	3.83 [0.00 – 8.13]	3.31 [1.00 – 8.13]	3.83 [0.00 – 8.13]	3.00 [1.50 – 8.13]
t_{last} [b]	h	12.0 [8.00 – 12.0]	12.0 [8.00 – 12.0]	12.0 [8.00 – 12.0]	12.0 [8.00 – 12.0]

Abbreviations: AUC=Area under the plasma concentration-time curve; BID=Twice daily; C_{max}=Maximum observed drug concentration; CV=Coefficient of variation; LLOQ=Lower limit of quantification; PK=Pharmacokinetic; PKS=Pharmacokinetic analysis set; t_{last}=Time of the last plasma concentration above LLOQ; t_{max}=Time to maximum observed drug concentration

a: n=11
b: Median [range]
Note: Units and values from the source data were transformed to mg/L and rounded to 3 significant digits manually.

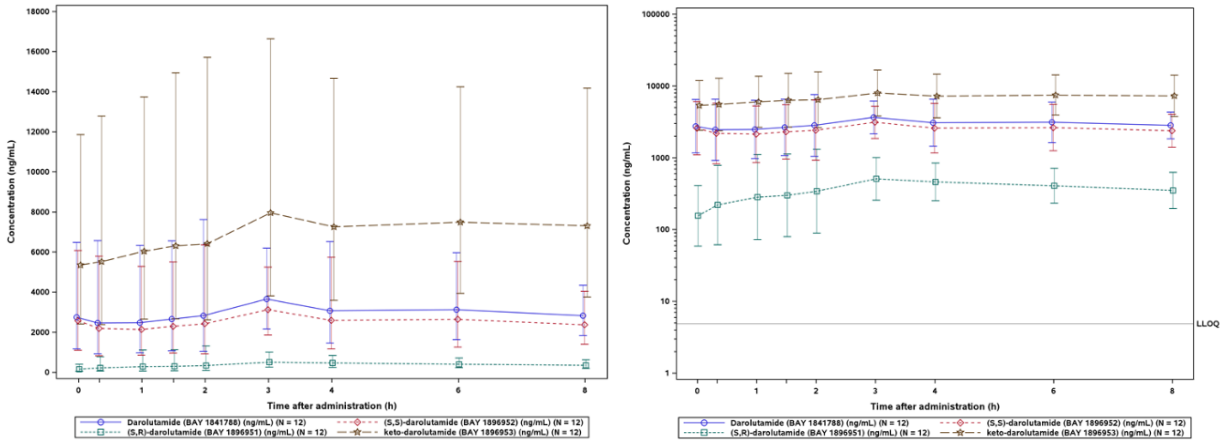


Figure 1: Geometric mean (+/− geom. StD) of darolutamide, (S,S)-darolutamide, (S,R)-darolutamide, and keto-darolutamide after multiple dose administration on the first day of docetaxel injection on linear scale (left) and semi-log scale (right), (PKS– Safety/PK lead-in)

China PK substudy

Among the 25 patients who met the PK population criterion in the China PK substudy, 14 patients were randomized into the darolutamide + docetaxel arm. PK parameters of darolutamide, (S,R)-darolutamide, (S,S)- darolutamide, and keto-darolutamide following single and multiple administration

Population PK modelling results for study 17777 ARASENS

Study number: CPMX50017 / report R-13408, report date 10 January 2022

Objectives

A previously developed population PK model for nmCRCP patients was used to describe the PK of darolutamide in mHSPC patients. In addition, the PK of (S,S)-darolutamide, (S,R)- darolutamide and keto-darolutamide were investigated and covariates potentially influencing their PK were examined. Moreover, individual docetaxel clearance and exposure on the basis of established literature models were evaluated. The potential of drug-drug interaction between darolutamide and docetaxel was analysed (refer to section "Pharmacokinetic interaction studies"). Furthermore, a meta-population PK analysis of study 17777 and study 17712 was done (presented below).

Data

Among the 1305 patients included in study 17777 ARASENS, 645 contributed to the darolutamide final population PK model analysis with 2496 concentrations of both (S,S)-darolutamide and keto-darolutamide and 2485 concentrations of (S,R)-darolutamide above the LLOQ. In addition, a total of 190 observations of both (S,S)- darolutamide and keto-darolutamide and 201 concentrations of (S,R)-darolutamide were below the LLOQ. In total, 1252 patients contributed to the PK assessment of docetaxel, with 2135 samples above the LLOQ and 225 concentration measures below the LLOQ, and 94 excluded.

A visualisation revealed non-normally distributed observed data. Box-Cox transformation were applied to evaluate if the transformed data more closely follow a normal distribution. Model building resumed with use of the Box-Cox transformed data. Re-estimation of parameter values could still not address bias in residuals on treatment day one. Attempts were made to include darolutamide concentrations below the LLOQ, but this constantly resulted in unstable parameter estimation. Therefore, it was

decided to omit data below LLOQ during model development. For model development where observations <LLOQ were included, the M3 method was used.

The median age of patients was 67 years (range 41 to 86 years) and the median body weight was 75.05 kg (range 39 to 144 kg). In total, 52.5 % of the patients were White, 35.9 % were Asian and 11.6% were categorized as other. Asian and "other" were combined to create the ethnicity covariate "white" vs "non-white". In total, 16.3 % of patients were from Mainland China, 9.9 % from Japan, 7.1 % from Korea and 2.5 % from Taiwan. Further to this, 16.5% patients were from the USA. The median baseline serum creatinine level was 0.88 mg/dL (range 0.4 to 2.39 mg/dL) and median estimated glomerular filtration rate at baseline was 92.75 mL/min (range 16.37 to 230.59 mL/min). The median baseline total bilirubin level was 0.53 mg/dL (range 0.04 to 1.95 mg/dL), median aspartate transaminase (AST) level was 24 U/L (range 7.95 to 79.8 U/L) and median alanine transaminase (ALT) was 24 U/L (range 1 to 161.6 U/L). In total, 92.2% of patients had normal hepatic function, 7.5% of patients had mild hepatic impairment and two patients had moderate hepatic impairment. The median baseline serum albumin level was 4.3 g/dL (range 2.4 to 6.15 g/dL) and the median baseline total protein level was 7.2 g/dL (range 5.2 to 9.11 g/dL).

Model development and results

The previously developed population PK model for nmCRCP patients was used. Parameters were re-estimated for study 17777 ARASENS data. Covariates were investigated using the forward inclusion (ΔOFV ≤10.828, $p < 0.001$, 1 degree of freedom) and backward elimination procedure (ΔOFV > +15.137, $p > 0.001$, 1 degree of freedom). Model selection criteria included commonly used methods like goodness-of-fit (GOF) plots, precision and plausibility of parameter estimates. For model qualification prediction-corrected visual predictive checks (pcVPC) were carried out (1000 replicates).

For docetaxel, a literature model was used (please refer to section "Pharmacokinetic interaction studies").

Parameter estimates of the final population PK model for darolutamide in study 17777 ARASENS are shown in **Table *6***. Bootstrap results are given in **Table *7***. VPCs are presented in **Figure *2***, **Figure *3***, and **Figure *4***. The model structure remained the same as the previously model structure. The population typical CL was 4.88 L/h (IIV = 41.5 %CV) and the total volume of distribution for all three analyses was 32.7 L (IIV = 117 %CV). ETA shrinkages were below 10.2 %. The absorption of darolutamide was described by several (inter-connected) processes due to the interconversion of the diastereomers via keto-darolutamide. Keto-darolutamide was more rapidly absorbed (KA3=0.26 h^{-1}) compared to (*S*,*R*)-darolutamide (KA1 = 0.06 h^{-1}) and R,S-darolutamide (KA2 = 0.006 h^{-1}). Following absorption, keto-darolutamide was rapidly interconverted back to (*S*,*R*)- and (mainly) (*S*,*S*)-darolutamide. As a result, the model predicted a much faster occurrence of (*S*,*R*)- and (*S*,*S*)-darolutamide, as reflected by the T_{max} (3.33 h (18.4%,1.35–4.59)) estimates, in the plasma/central compartment as the estimated KA1 and KA2 values might suggest. Parameter KRET (estimate: 0.475) represented the ratio between the transformation rate of (S,S)- or (S,R)-darolutamide to keto-darolutamide and the transformation rate of keto-darolutamide back to (S,S)- or (S,R)-darolutamide. It informed about the net transformation of darolutamide to keto-darolutamide or vice versa. Age, Japanese, and Chinese were identified as statistically significantly covariates. As such, CL increased by approximately 26.3 % for patients under 65 versus patients ≥ 65 years, Japanese having a CL 32 % lower than patients from the rest of regions (excluding Mainland China) and patients in Mainland China having a CL 19.7% lower than patients from the rest of regions (excluding Japan). Residual variability varied between 14 – 35 %. Relative standard error (RSE) was below 26 %.

Table 6: Parameter estimates of the final population PK model for darolutamide

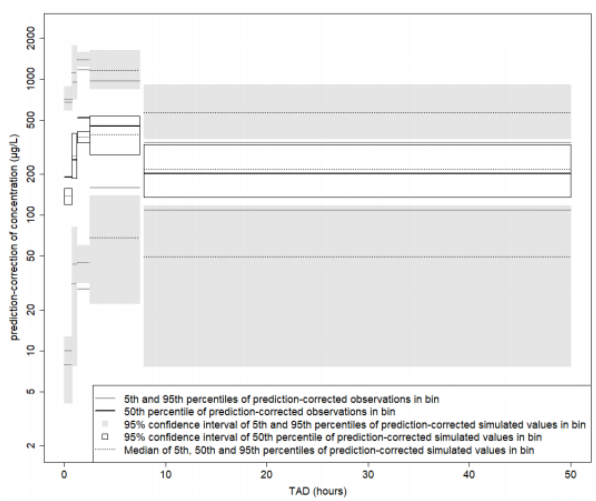
Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
KTR	h^{-1}	17.2	4.83	15.6	18.9	Transit compartment rate
KA1	h^{-1}	0.0601	7.26	0.0515	0.0686	Absorption rate constant for (*S,R*)-darolutamide
KA2	h^{-1}	0.00556	9.49	0.00452	0.00659	Absorption rate constant for (*S,S*)-darolutamide
KA3	h^{-1}	0.262	5.28	0.235	0.289	Absorption rate constant for keto-darolutamide
CL_{pop}[1]	L/h	4.88	2.78	4.62	5.15	Clearance for a typical patient with AGE ≥ 65 and not from Asia
V_{pop}[1]	L	32.7	6.68	28.4	37.0	Volume of distribution for all three analytes in a typical patient
KMETSR	h^{-1}	0.763	18.3	0.489	1.04	Rate constant for conversion between (*S,R*)-darolutamide and keto-darolutamide
KMETSS	h^{-1}	6.76	25.5	3.38	10.1	Rate constant for conversion between (*S,S*)-darolutamide and keto-darolutamide
KRET	-	0.475	0.970	0.466	0.484	Scaling parameter for rate of conversion from keto to (*S,R*) and (*S,S*) darolutamide
θ_{RR}	-	-1.94	1.12	-1.99	-1.90	RR
θ_{AGE}	-	0.263	18.4	0.168	0.358	Parameter describing the influence of a patient being younger than 65 on CL
θ_{JPN}	-	-0.322	12.7	-0.403	-0.242	Parameter describing the influence of Japan geographic region on CL
θ_{CHINA}	-	-0.197	23.1	-0.287	-0.108	Parameter describing the influence of Mainland China geographic region on CL
Random effects: Inter-individual variability (OMEGA)						
CL (ω^2)	-	0.159	5.88	0.141	0.177	Inter-individual variability on CL
CL (CV)[2]	%	41.5		38.9	44.0	
CL (Sh)[3]	%	12.5				
V (ω^2)	-	0.866	7.33	0.742	0.991	Inter-individual variability on V
V (CV)[2]	%	117		105	130	
V (Sh)[3]	%	10.2				
Residual error (SIGMA)						
(S,R) (σ^2)	-	34.9	2.99	32.9	37.0	Additive residual error on Box-Cox scale for (*S,R*)-darolutamide
(S,R) (CV)[4]	%	21.5		20.8	22.1	
(S,S) (σ^2)	-	49.5	3.09	46.5	52.5	Additive residual error on Box-Cox scale for (*S,S*)-darolutamide
(S,S) (CV)[4]	%	14.1		13.7	14.6	
Keto (σ^2)	-	169	3.62	157	181	Additive residual error on Box-Cox scale for keto-darolutamide
Keto (CV)[4]	%	17.8		17.2	18.4	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
1 Apparent PK parameter, equivalent to CLpop/F and Vpop/F
2 The coefficient of variation (CV) is calculated as 100·SQRT(EXP(OMEGA2)-1)
3 Shrinkage (Sh) calculated as 100·(1-standard deviation of individual eta estimates/ω)
4 The coefficient of variation (CV) for SIGMA is calculated as 100·SQRT(SIGMA2)/μ for μ = 27.5, 49.8 and 73.0, which corresponds to a concentration of 500 µg/L for (*S,R*)-darolutamide, 2000 µg/L for (*S,S*)-darolutamide and 5000 µg/L for keto-darolutamide, respectively.

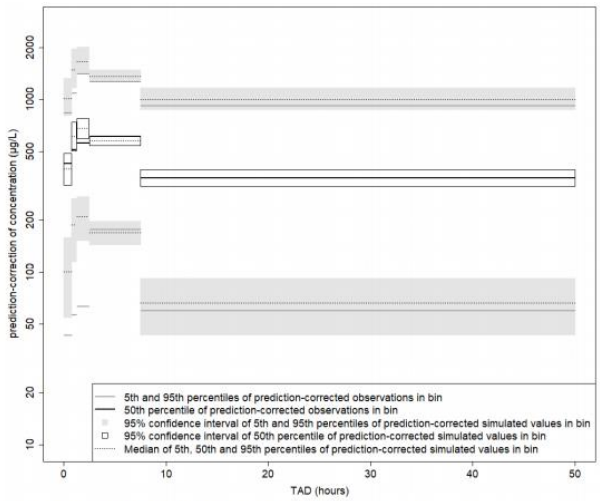
Table 7: Parameter estimates of the final population PK model including bootstrap results

Parameter	Unit	Estimate	LLCI	LLCI - bootstrap	ULCI	ULCI - bootstrap
Fixed effects (THETA)						
KTR	h^{-1}	17.2	15.6	14.5	18.9	20.0
KA1	h^{-1}	0.0601	0.0515	0.0373	0.0686	0.0893
KA2	h^{-1}	0.00556	0.00452	0.00466	0.00659	0.00658
KA3	h^{-1}	0.262	0.235	0.174	0.289	0.383
CL_{pop}[1]	L/h	4.88	4.62	4.60	5.15	5.19
V_{pop}[1]	L	32.7	28.4	20.9	37.0	45.8
KMETSR	h^{-1}	0.763	0.489	0.636	1.04	0.877
KMETSS	h^{-1}	6.76	3.38	5.09	10.1	9.50
KRET	-	0.475	0.466	0.458	0.484	0.493
θ_{RR}	-	-1.94	-1.99	-2.02	-1.90	-1.88
θ_{AGE}	-	0.263	0.168	0.185	0.358	0.366
θ_{JPN}	-	-0.322	-0.403	-0.406	-0.242	-0.227
θ_{CHINA}	-	-0.197	-0.287	-0.258	-0.108	-0.126
Random effects: Inter-individual variability (OMEGA)						
CL (ω^2)	-	0.159	0.141	0.130	0.177	0.190
V (ω^2)	-	0.866	0.742	0.688	0.991	1.16
Residual error (SIGMA)						
(S,R) (σ^2)	-	34.9	32.9	31.6	37.0	37.4
(S,S) (σ^2)	-	49.5	46.5	44.2	52.5	55.4
Keto (σ^2)	-	169	157	155	181	184

Abbreviations are described in Module 5.3.3.5, Report R-13408, Table 14-8
LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
LLCI – bootstrap: 2.5th percentile of parameter estimate from a bootstrap with 463 successful iterations.
ULCI – bootstrap: 97.5th percentile of parameter estimate from a bootstrap with 463 successful iterations.

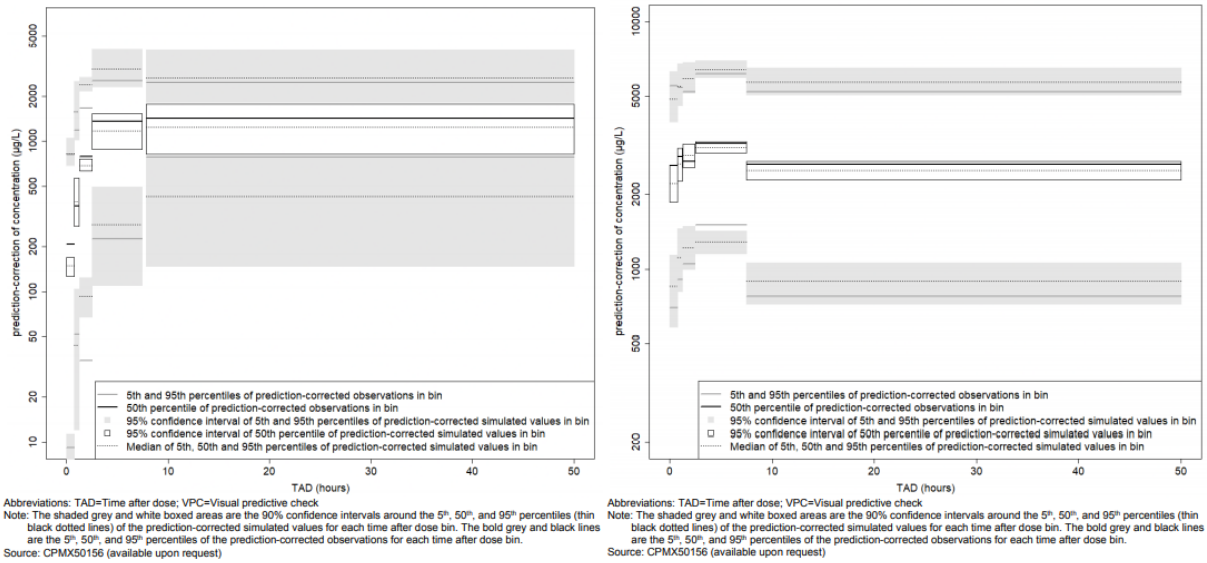


Abbreviations: TAD=Time after dose; VPC=Visual predictive check
Note: The shaded grey and white boxed areas are the 90% confidence intervals around the 5th, 50th, and 95th percentiles (thin black dotted lines) of the prediction-corrected simulated values for each time after dose bin. The bold grey and black lines are the 5th, 50th, and 95th percentiles of the prediction-corrected observations for each time after dose bin.
Source: CPMX50156 (available upon request)



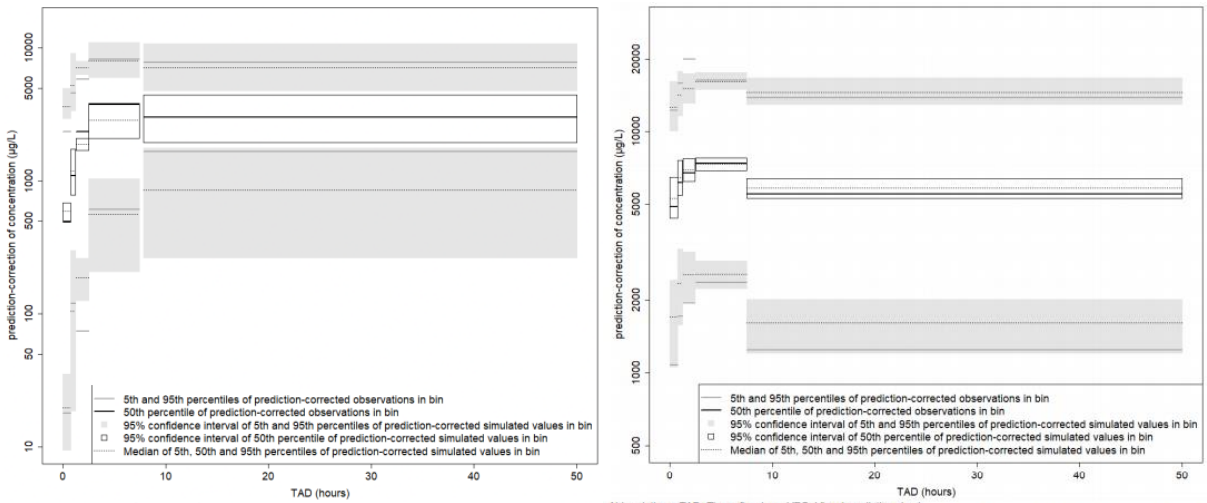
Abbreviations: TAD=Time after dose; VPC=Visual predictive check
Note: The shaded grey and white boxed areas are the 90% confidence intervals around the 5th, 50th, and 95th percentiles (thin black dotted lines) of the prediction-corrected simulated values for each time after dose bin. The bold grey and black lines are the 5th, 50th, and 95th percentiles of the prediction-corrected observations for each time after dose bin.
Source: CPMX50156 (available upon request)

Figure 2: Prediction-corrected VPC for (S,R)-darolutamide for Day 1(left) and Day > 1 (right)



Abbreviations: TAD=Time after dose; VPC=Visual predictive check
Note: The shaded grey and white boxed areas are the 90% confidence intervals around the 5th, 50th, and 95th percentiles (thin black dotted lines) of the prediction-corrected simulated values for each time after dose bin. The bold grey and black lines are the 5th, 50th, and 95th percentiles of the prediction-corrected observations for each time after dose bin.
Source: CPMX50156 (available upon request)

Figure 3: Prediction-corrected VPC for (S,S)-darolutamide for Day 1(left) and Day > 1 (right)



Abbreviations: TAD=Time after dose; VPC=Visual predictive check
Note: The shaded grey and white boxed areas are the 90% confidence intervals around the 5th, 50th, and 95th percentiles (thin black dotted lines) of the prediction-corrected simulated values for each time after dose bin. The bold grey and black lines are the 5th, 50th, and 95th percentiles of the prediction-corrected observations for each time after dose bin.
Source: CPMX50156 (available upon request)

Figure 4: Prediction-corrected VPC for keto-darolutamide for Day 1(left) and Day > 1 (right)

Population PK model-derived exposure for all analytes are summarised in Table 8, and C_{min}, C_{max}, and AUC_{0-12} are provided in Table 9 and Table 10. The median model-based effective half-life for darolutamide, keto-darolutamide, (S,R)-darolutamide and (S,S)-darolutamide were 15.4 h (62 %CV), 16 h (63.2 %CV), 9.53 h (76.2 %CV), and 16.9 h (58.8 %CV), respectively. Geometric mean t_{max} ranged between 2.24 h and 3.81 h (11 – 19.5 %CV).

Table 8: Summary of geometric mean (%CV) PK parameters as steady-state in study 17777

	Darolutamide (n=652)	(*S*,*R*)-darolutamide (n=652)	(*S*,*S*)-darolutamide (n=652)	Keto-darolutamide (n=652)
C_{max}, mg/L	3.84 (35.6%)	0.711 (39.1)	3.16 (36.3%)	7.53 (36.3%)
t_{max}, h	3.33 (18.4%)	2.24 (11.2%)	3.81 (19.5%)	3.66 (20.3%)
AUC(0–12), h·mg/L	38.2 (39.1%)	5.85 (35.9%)	32.3 (40.1%)	76.0 (41.1%)
Effective $t_{1/2}$, h	18.4 (62.0%)	10.9 (76.2%)	20.5 (58.8%)	19.0 (63.2%)

AUC(0–12)=Area under the plasma concentration-time curve from time 0 to 12 hours; C_{max}=Peak concentration; CV=Coefficient of variation; PK=Pharmacokinetic; PopPK=Population pharmacokinetics; t_{max}=Time to peak concentration; $t_{1/2}$=Effective half-life

Table 9: Population PK model-derived exposure of darolutamide and keto-darolutamide in study 17777 ARASENS

Statistic	Darolutamide C_{min}[a] [mg/L]	Darolutamide C_{max}[b] [mg/L]	Darolutamide AUC(0-12)[c] [h·mg/L]	Keto-C_{min}[a] [mg/L]	Keto-C_{max}[b] [mg/L]	Keto-AUC(0-12)[c] [h·mg/L]
N	652	652	652	652	652	652
Minimum	0.295	0.749	6.19	0.566	1.38	11.7
5th Percentile	1.09	2.17	20.5	2.09	4.27	39.5
Median	2.43	3.9	38.1	4.93	7.49	76.8
95th Percentile	4.84	6.45	67.9	10	12.8	138
Maximum	10.5	11.6	135	22	24.1	280
Arithmetic Mean	2.61	4.06	40.8	5.34	7.98	81.8
Geometric Mean	2.35	3.84	38.2	4.75	7.53	76
Geometric SD	1.6	1.41	1.46	1.65	1.42	1.48
Geometric CV (%)	49.8	35.6	39.1	53.2	36.3	41.1

[a] Calculated trough concentration after 15 days of nominal BID dosing at 600mg.
[b] Calculated maximum concentration after 15 days of nominal BID dosing at 600mg.
[c] Calculated AUC from 0 to 12 h after 15 days of nominal BID dosing at 600mg.

Table 10: Population PK model-derived exposure of (S,R)-darolutamide and (S,S)-darolutamide in study 17777 ARASENS

Statistic	(*S*,*R*) C_{min}[a] [mg/L]	(*S*,*R*) C_{max}[b] [mg/L]	(*S*,*R*) AUC(0-12)[c] [h·mg/L]	(*S*,*S*) C_{min}[a] [mg/L]	(*S*,*S*) C_{max}[b] [mg/L]	(*S*,*S*) AUC(0-12)[c] [h·mg/L]
N	652	652	652	652	652	652
Minimum	0.0291	0.141	1.11	0.266	0.582	5.08
5th Percentile	0.103	0.388	3.35	0.973	1.8	17
Median	0.279	0.72	5.87	2.14	3.14	32.4
95th Percentile	0.585	1.26	9.89	4.25	5.39	58.3
Maximum	1.3	1.91	17.8	9.2	10.1	117
Arithmetic Mean	0.304	0.761	6.2	2.31	3.35	34.6
Geometric Mean	0.266	0.711	5.85	2.08	3.16	32.3
Geometric SD	1.72	1.46	1.42	1.59	1.42	1.47
Geometric CV (%)	58.4	39.1	35.9	48.9	36.3	40.1

a Calculated trough concentration after 15 days of nominal BID dosing at 600mg.
b Calculated maximum concentration after 15 days of nominal BID dosing at 600mg.
c Calculated AUC from 0 to 12 h after 15 days of nominal BID dosing at 600mg.

Population PK modelling meta-analysis of study ARASENS and study ARAMIS (17712)

Study 17712 ARAMIS was the pivotal phase 3 monotherapy Study for nmCRPC patients treated with darolutamide 600 mg BID (refer to the initial Marketing Authorisation Application (MAA).

Table 11 presents the geometric mean phase 3 model-predicted PK parameters for study 17712 as presented in the initial MAA. The population PK model-predicted exposure for (S,R)-darolutamide, (S,S)-darolutamide and keto-darolutamide was different in Study 17777 (Table 8) compared to that of Study 17712 (Table 11).

Table 11: Geometric mean (CV [%]), PK parameters at steady state in Study 17712 using the selected Phase 3 population PK model (Study 18651)

	Darolutamide (n=388)	(*S*,*R*)-darolutamide (n=388)	(*S*,*S*)-darolutamide (n=388)	Keto-darolutamide (n=388)
C_{max}, µg/mL	4.786 (30.9)	0.682 (22)	4.212 (32.1)	8.475 (35.4)
t_{max}, h	3.64 (4.4)	1.84 (3.5)	4.73 (3.5)	2.06 (3.3)
AUC(0-12), µg·h/mL	52.817 (33.9)	5.499 (33.2)	47.238 (34.5)	87.640 (42.1)
Effective $t_{1/2}$, h	19.6 (29.7)	8.92 (36.5)	21.9 (29.6)	20.0 (37.9)

Abbreviations: AUC(0-12) = area under the plasma concentration time curve from time 0 to 12 hours; C_{max} = peak concentration; CV% = coefficient of variation; PK = pharmacokinetics; popPK = population pharmacokinetics; t_{max} = time to peak concentration; $t_{1/2}$ = half-life.

This meta-analysis was done using pooled data from study 17777 ARASENS and study 17712 ARMAIS to (1) evaluate the contribution of pre-defined covariates to the variability in darolutamide PK in the combined data, and (2) to assess the extent to which differences in darolutamide exposure between both studies is accounted for by differences in population characteristics.

The population PK base model for Study 17777 was used and inter-individual variability (IIV) and covariates were re-estimated. The ratio of the model-derived geometric mean AUC(0- 12)ss value for Study 17777 versus 17712 was calculated for each analyte (bootstrap analysis). Additional IIV were identified for the rate at which keto is transformed to (S,S)-darolutamide or (S,R)-darolutamide (KRET) and RR as well as the following covariates: Age, Asian, and Japanese on CL, China on V, serum creatinine at baseline, body weight on KRET (i.e. scaling parameter for rate of conversion from keto to (S,R) and (S,S) darolutamide), and age, and AST on RR (i.e. conversion ratio of keto-darolutamide to either (S,R)-darolutamide or (S,S)- darolutamide). Parameter estimates of the population PK meta-analysis are provided in Table 12.

Table 12: Parameter estimates of the population PK meta-analysis, studies 17777 and 17712

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
KTR	h^{-1}	18.2	3.49	17	19.5	Transit compartment rate constant
KA1	h^{-1}	0.0571	4.51	0.0521	0.0621	Absorption rate constant for (*S,R*)-darolutamide
KA2	h^{-1}	0.00791	4.08	0.00728	0.00855	Absorption rate constant for (*S,S*)-darolutamide
KA3	h^{-1}	0.256	4.39	0.234	0.279	Absorption rate constant for keto-darolutamide
CL_{pop}[1]	L/h	5.09	1.75	4.91	5.26	Clearance for a typical patient
V_{pop}[1]	L	37.4	4.84	33.8	40.9	Volume of distribution for all three analytes in a typical patient
KMETSR	h^{-1}	0.615	11.9	0.472	0.758	Rate constant for conversion between (*S,R*)-darolutamide and keto-darolutamide
KMETSS	h^{-1}	4.39	15.9	3.02	5.77	Rate constant for conversion between (*S,S*)-darolutamide and keto-darolutamide
θ_{KRET}	-	0.52	1.22	0.508	0.533	Scaling parameter for rate of conversion from keto to (*S,R*) and (*S,S*) darolutamide
θ_{RR}	-	-2.24	1.27	-2.29	-2.18	Conversion ratio of keto-darolutamide to either (*S,R*)-darolutamide or (*S,S*)-darolutamide
$\theta_{AGE,CL}$		-0.0182	8.98	-0.0214	-0.015	Age on clearance

θ_{WGHT}		0.522	9.81	0.422	0.622	Weight on KRET
θ_{ASIAN}		-0.173	17.5	-0.232	-0.114	Asian on CL
$\theta_{AGE,RR}$		-0.0146	16.6	-0.0193	-0.00983	Age on RR
θ_{CHN}		-0.373	14.9	-0.483	-0.264	China on V
θ_{AST}		0.0106	23.4	0.00574	0.0154	AST on RR
θ_{JPN}		-0.192	22.5	-0.277	-0.107	JPN on CL
θ_{SCRE}		0.179	24.4	0.0933	0.265	SCRE on KRET
Random effects: Inter-individual variability (OMEGA)						
CL (ω^2)	-	0.156	4.60	0.142	0.17	Inter-individual variability on CL
CL $(CV)^2$	%	41		39.0	43.0	
CL $(Sh)^3$	%	8.63				
V (ω^2)	-	0.722	5.60	0.642	0.801	Inter-individual variability on V
V $(CV)^2$	%	103		94.9	111	
V $(Sh)^3$	%	13.66				
KRET (ω^2)	-	0.0569	7.32	0.0488	0.0651	Inter-individual variability on KRET
KRET $(CV)^2$	%	24.2		22.4	25.9	
KRET $(Sh)^3$	%	30.1				
RR (ω^2)	-	0.137	9.70	0.111	0.164	Inter-individual variability on RR
RR $(CV)^2$	%	16.6		14.9	18.1	
RR $(Sh)^3$	%	39.61				
Residual error (SIGMA)						
(S,R) (σ^2)	-	27.0	2.19	25.8	28.2	Additive residual error on Box-Cox scale for (S,R)-darolutamide
(S,R) $(CV)^4$	%	18.9		18.5	19.3	
(S,S) (σ^2)	-	42.0	1.77	40.5	43.4	Additive residual error on Box-Cox scale for (S,S)-darolutamide
(S,S) $(CV)^4$	%	13.0		12.8	13.2	
Keto (σ^2)	-	125	2.33	119	131	Additive residual error on Box-Cox scale for keto-darolutamide
Keto $(CV)^4$	%	15.3		14.9	15.7	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)

2.3.2.4. Special populations

Information on special populations were updated based on a submitted population PK analysis of study 17777 ARASENS in patients with mHSPC (Study number: CPMX50017 / report R-13408, report date 10 January 2022).

Renal impairment

The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC reported a mean 1.11-fold (90 % CI: 1.06 – 1.17), 1.27-fold (90 % CI: 1.14 – 1.41), and 2.6-fold (one patient) higher exposure (AUC) of darolutamide in patients with mild, moderate, and severe renal impairment

compared to patients with normal renal function. These results are consistent with previous findings from study 17712 ARAMIS in patients with nmCRPC.

No new information was provided regarding patients with end-stage renal disease receiving dialysis.

Hepatic impairment

The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC reported a similar exposure in patients with mild hepatic impairment (mean geometric ratio 0.977 [90 % CI: 0.879 – 1.08]) compared to patients with normal hepatic function. These results are consistent with previous findings from study 17712 ARAMIS in patients with nmCRPC.

Gender

Not applicable.

Race/Ethnicity

The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC reported a higher increase in exposure ($AUC_{(0-12)ss}$) for Japanese patients (mean ratio compared to rest of regions = 1.56 (90%CI: 1.43 – 1.70) as compared to the previous analysis of data from study 17712 ARAMIS (mean ratio compared to rest of regions =1.42 (90%CI: 1.33 - 1.53)).

Body weight

Results for body weight effects on exposure of darolutamide from the population PK analysis using data from Study 17777 ARASENS in patients with mHSPC were consistent with previous findings from study 17712 ARAMIS in patients with nmCRPC.

Elderly

The population PK analysis using data from Study 17777 ARASENS in patients with mHSPC reported that mean exposure ($AUC_{(0-12)ss}$) for patients aged 65 - <75 years was about 1.28-fold (90%CI: 1.22–1.34) higher and for patients aged 75 - < 85 about 1.34-fold (90% CI: 1.25 – 1.49) higher compared to patients aged < 65 years. The ratio was similar for patients aged ≥85 years compared to the age group 75 - < 85. However only three patients were aged above 85 years of age.
Results for the age group 65 - <75 years were slightly lower compared to those from study 17712 ARAMIS in patients with nmCRPC, but were generally comparable and consistent.

2.3.2.5. Pharmacokinetic interaction studies

Docetaxel population PK model

Study number: CPMX50017 / report R-13408, report date 10 January 2022

Individual docetaxel clearance and exposure were investigated using an established literature population PK model. Docetaxel clearance between the two treatment arms (with or without darolutamide) in study 17777 ARASENS were assessed and the correlation between darolutamide and docetaxel clearance on an individual level was evaluated.

Overall, 1152 patients with 2135 plasma PK samples above and 225 samples below LLOQ contributed to the analysis. The final population PK model for docetaxel is a 3-compartment model with linear elimination. The parameters were re-estimated based on study 17777 PK data. Parameter estimates from the final model for study 17777 are listed in Table 13. All covariates in the docetaxel literature model were identified for study 17777 data, with the exception of α1-acid glycoprotein (AAG). AAG was fixed to the median value provided in the literature. The remaining covariates on CL were body surface area (BSA, calculated using the DuBois method), albumin, age and hepatic function (called HEP12).

Based on the GOF plots DV versus Population Predicted Value (PRED) and pc-VPC, the population PK model of docetaxel is biased on the structural (PRED) predictions. Taking into account that the objective of the docetaxel population PK modelling was to estimate individual clearance and exposure of docetaxel in Study 17777, the bias on the population level was considered acceptable. The GOF plots for the individual weighted residuals (IWRES) were considered to show a lack of bias in the individual predictions, and it was concluded that the literature model was fit-for-purpose to estimate individual clearance and exposure of docetaxel in Study 17777.

Summary statistics of individual estimates of docetaxel clearance stratified by treatment arm are presented in Table 14 and box plots showing docetaxel concentrations versus time after dose are stratified by treatment arm are presented in Figure 5.

Table 13: Parameter values for the docetaxel literature model

Parameter	Unit	Value	Description
Fixed effects (THETA)			
θ_{CL}	L·m²/h	22.1	
θ_{AAG}	-	-3.55	parameter giving the value to be adjusted by covaraites for clearance
θ_{AGE}	-	-0.095	parameter describing the influence of AAG on clearance parameter describing the influence of AGE on clearance
θ_{ALB}	-	0.0225	parameter describing the influence of ALB on clearance parameter describing the influence of hepatic impairment on clearance
θ_{HEP12}	-	0.334	apparent volume of central compartment
V_{1pop}	L	8.31	intercompartmental rate constant
K_{12}	h^{-1}	1.07	intercompartmental rate constant
K_{21pop}	h^{-1}	1.74	intercompartmental rate constant
K_{13pop}	h^{-1}	1.28	intercompartmental rate constant
K_{31pop}	h^{-1}	0.0787	
Random effects: Inter-individual variability (OMEGA)			
CL (ω^2)	-	0.335	Inter-individual variability on CL
V_1 (ω^2)	-	0.561	Inter-individual variability on V_1
K_{21} (ω^2)	-	1.31	Inter-individual variability on K_{21}
K_{13} (ω^2)	-	0.477	Inter-individual variability on K_{13}
K_{31} (ω^2)	-	0.147	Inter-individual variability on K_{31}
Residual error (SIGMA)			
σ^2	-	0.205	Additive residual error

Table 14: Summary statistics of individual estimates of docetaxel clearance by treatment arm, study 17777 ARASENS

Statistic	Control arm Docetaxel clearance [L·m²/h]	Darolutamide arm Docetaxel clearance [L·m²/h]
N	637	642
Minimum	9.58	7.86
5th Percentile	14.3	14.7
Median	26.5	28
95th Percentile	49.2	52.1
Maximum	79	76.3
Arithmetic Mean	28.2	29.8
Geometric Mean	26.5	27.8
Geometric SD	1.43	1.46
Geometric CV (%)	36.6	38.9
Geometric Mean ratio[a]	-	1.05 (1.01 – 1.08)

[a] Geometric mean ratio 90% CIs were calculated using a bootstrap approach

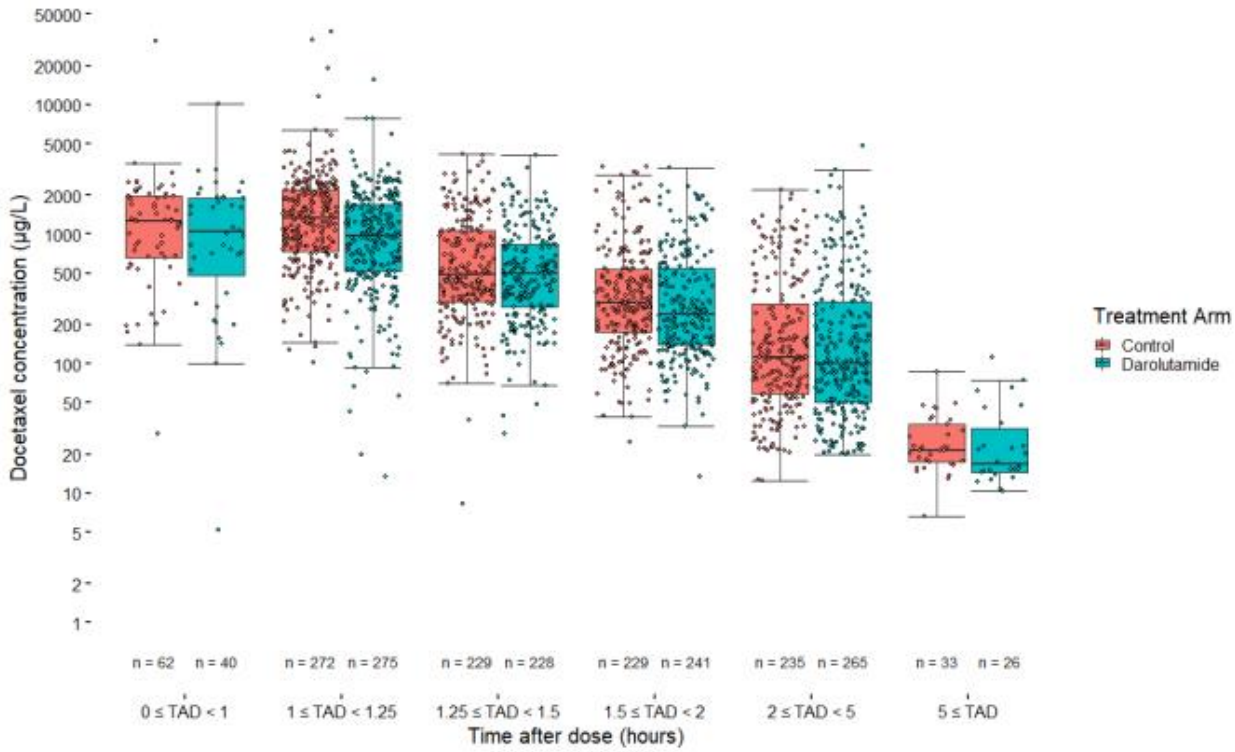


Figure 5: Docetaxel concentration data stratified by treatment arm, study 17777 ARASENS

2.3.3. PK/PD modelling

Population PK/PD modelling for efficacy (study 17777 ARASENS)

Study number: CPMX50018 / report R-13397, report date 31 December 2021

An exploratory population pharmacodynamic (PD) analysis of change in prostate specific antigen over time in patients with metastatic hormone-sensitive prostate cancer of study 17777.

Objectives

This study aimed to describe the change in prostate specific antigen (PSA) over time by means of a semi-mechanistic model, investigate covariates, and evaluate the multivariate relationship between darolutamide and/or active metabolite exposure, docetaxel exposure and the change in PSA over time. In addition, the potential relationship between the change in testosterone over time and darolutamide exposure was investigated using exploratory analysis. Furthermore, the association between the time-course of PSA and overall survival was visualised (means of Kaplan Meier curves per quartile of change in PSA and curves per quartile of darolutamide exposure).

Data and methods

Data below LLOQ (BLQ) under treatment were included in the dataset. Measurements with no recorded sample time and vice versa were excluded. Missing continuous and categorical baseline covariate data were in general either filled with the population median value or most frequent category across study 17777. The dataset considered for this analysis contained all patients of study 17777 who received at least one dose of study drug, either darolutamide or control.

Nonlinear mixed-effects modelling using NONMEM software version 7.4.3 was used.

Exposure variables were calculated based on the population PK models described in report CPMX50017 / report R-13408, report date 10 January 2022. Different exposure variables were tested.

A previous developed model was used as a starting point to investigate the PKPD relationship with PSA: BAY 1841788 (darolutamide) / 19792. Exploratory population pharmacodynamic analysis of change in prostate specific antigen over time in studies 17712, 17829 and 17830. M&S Report R-12788, Version 1.0, dated 08 JAN 2019. The base model described the growth of prostate cancer cells by means of a tumour cell proliferation and kill rate. Furthermore, the model described the secretion of PSA in the blood by the tumour cells and the elimination of PSA from the blood. Covariates were investigated using the forward inclusion ($\Delta OFV \leq 6.67$, $p < 0.01$, 1 degree of freedom) and backward elimination procedure ($\Delta OFV > +10.828$, $p > 0.001$, 1 degree of freedom). Model evaluation and qualification was done using generally applied methods (e.g. GOF plots, precision of parameter estimates, VPCs). The final covariate model was used to calculate the predicted reduction in PSA from baseline at different time-points. It was assumed that PSA concentrations in blood were at steady state at the start of treatment.

Change of testosterone over time was investigated using exploratory plots (i.e. spaghetti plots).

The potential relationships between darolutamide exposure and overall survival was explored through different Kaplan Meier plots.

Instantaneous concentration of docetaxel was not tested due to only a single PSA data-point being available during the docetaxel phase for the majority of patients. Instead, four docetaxel covariates were tested: Total docetaxel dose, average docetaxel dose, total docetaxel AUC and average docetaxel AUC.

Results

The darolutamide exposure variables at steady state for the 647 patients of study 17777 (initial data) and docetaxel exposure variables for the 1280 patients of study 17777 (initial data) were predicted based on the population PK models as described in CPMX50017 / report R-13408, report date 10 January 2022.

- PSA

Data used in the inference of the selected covariate model onto the final data, resulting in the final covariate model, included 13994 PSA observations from 1302 patients who received at least one dose of study drug. Compared to the initial data, one patient was removed from the data due to a serious data breach. Overall, 12693 post-baseline PSA observations were used for model inference. Of these 12693 post-baseline PSA observations, 3726 (29.4%) were below the LLOQ.

Parameter estimates of the final PD model for PSA are listed in Table 15.

Table 15: Parameter estimates of the final PD model for PSA

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
k_{out}	day^{-1}	0.046	FIX			Rate constant for elimination of prostate tumor cells
d_{eli}	day^{-1}	0.23	FIX			Rate constant for elimination of PSA from the blood
θ_{rpro}	day^{-1}	0.0533	0.938	0.0523	0.0543	Rate of prostate tumor cell proliferation in a typical patient
θ_{EM}	log(µg/L)	6.02	2.56	5.72	6.33	Value of E_M for a typical patient in the control arm
$1000 \cdot \theta_{ER}$	day^{-1}	7.89	3.79	7.31	8.48	Decay rate constant for E_M in a typical patient
$\theta_{TREAT,rpro}$	-	-0.103	8.65	-0.121	-0.0857	Fractional change in r_{pro} for patients in the darolutamide arm
$\theta_{TREAT,EM}$	-	0.281	12.8	0.21	0.352	Fractional change in E_M for patients in the darolutamide arm
$1000 \cdot \theta_{HGB}$	(g/mL)$^{-1}$	-24.8	11.2	-30.2	-19.3	Parameter describing the influence of hemoglobin on r_{pro}
$1000 \cdot \theta_{PSABL}$	(µg/L)$^{-1}$	0.16	5.89	0.142	0.179	Parameter describing the influence of baseline PSA on E_M
θ_{ALP2}	-	0.0515	20.2	0.0311	0.0719	Parameter describing the influence of 2nd quartile of ALP on r_{pro}
θ_{ALP3}	-	0.069	16.7	0.0465	0.0916	Parameter describing the influence of 3rd quartile of ALP on r_{pro}
θ_{ALP4}	-	0.109	11.7	0.0839	0.134	Parameter describing the influence of 4th quartile of ALP on r_{pro}
$\theta_{ALPGTMED}$	-	0.247	20.2	0.149	0.344	Parameter describing the influence ALP > median ALP on E_R
θ_{CHINA}	-	0.299	25	0.153	0.446	Parameter describing the influence of geographical region China on E_R
θ_{JPN}	-	-0.0669	18.6	-0.0912	-0.0425	Parameter describing the influence of geographical region Japan on r_{pro}
θ_{KOR}	-	-0.0605	18.6	-0.0826	-0.0384	Parameter describing the influence of geographical region Korea on r_{pro}
Random effects: Inter-individual variability (OMEGA)						
r_{pro} (ω^2)	-	0.0325	6.30	0.0285	0.0365	IIV on r_{pro}.
r_{pro} (CV[d])	%	18.2		17.0	19.3	
r_{pro} (Sh[e])	%	17.5				
r_{pro} and E_M (ω^2)	-	0.0486	10.5	0.0386	0.0586	Off diagonal term of OMEGA block
E_M (ω^2)	-	0.271	6.32	0.237	0.304	IIV on E_M.
E_M (CV[d])	%	55.7		51.7	59.6	
E_M (Sh[e])	%	27.2				
r_{pro} and E_R (ω^2)	-	-0.0448	16.2	-0.0591	-0.0305	Off diagonal terms of OMEGA block
E_M and E_R (ω^2)	-	-0.238	10.8	-0.288	-0.188	
E_R (ω^2)	-	0.640	7.54	0.545	0.734	IIV on E_R.
E_R (CV[d])	%	94.6		85.1	104	
E_R (Sh[e])	%	24.2				
Residual error (SIGMA)						
Resid (σ^2)	-	0.315	0.625	0.312	0.319	Additive residual error on log scale
Resid CV[f]	%	24.4		24.3	24.6	

[a] RSE = relative standard error (100·SE/estimate)
[b] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)
[c] ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
[d] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[e] Shrinkage (Sh) is calculated as 100·(1-standard deviation of individual eta estimates/ω) where individual eta estimates only contribute for patients with quantified post-baseline PSA observations.
[f] The coefficient of variation (CV) is calculated as 100·SQRT(σ^2)/2.3 which is the CV for an observation of 2.3 on log scale, which corresponds to a PSA concentration of 10 ng/mL.

Darolutamide and docetaxel exposure did not result in a statistically significant covariate in the PD model. Baseline PSA, haemoglobin, alkaline phosphatase and three Asian geographic region China, Japan, and Korea, were found to influence PSA time course.

Darolutamide-treated patients were found to be associated with a greater and longer lasting PSA reduction compared to control patients. The difference in the fraction of patients with ≥ 90% reduction in PSA from baseline at week 24 between darolutamide-treated and control groups is consistent in sub-groups defined by age, race, geographical region, renal function, hepatic function and bodyweight. Also, dose reductions or interruptions for darolutamide-treated patients are not expected to affect PSA response. The PSA time-course was consistent over the darolutamide exposure range after 600 mg BID. Differences in docetaxel exposure were not found to influence PSA time course.

Despite of some deficiencies in the model, overall, it is considered to support darolutamide efficacy in patients from study 17777 ARASENS.

- Testosterone

Data used in the exploratory model-free analysis of the time-course of total testosterone included 11240 observations from 1303 patients. Of these, 8792 (78.2%) were below the LLOQ. The data file also included 2246 free testosterone observations from 597 patients. Of these, 91 (4.05%) were below the LLOQ. Spaghetti plot of the time-course of total testosterone were carried out. No differences in the time-course of total testosterone between darolutamide-treated and control patients were observed.

- Kaplan Meier plots of overall survival

Exploratory Kaplan Meier plots of overall survival were carried out and indicated:

- There was no indication of an association between overall survival and darolutamide exposure within darolutamide-treated patients

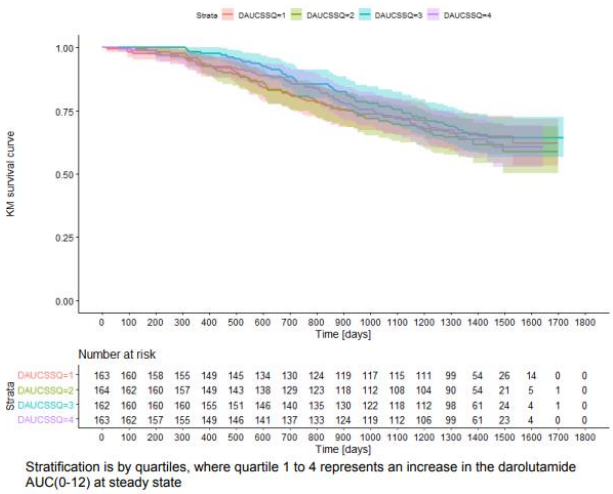


Figure 6: Overall survival stratified by quartiles of darolutamide $AUC_{(0-12)ss}$

Population PK/PD modelling for safety (study 17777 ARASENS)

Study number: CPMX50020 / report R-14071, report date 12 January 2022

Exploratory exposure-response analysis of relevant safety events in patients with metastatic hormone-sensitive prostate cancer of study 17777.

Objectives

Evaluate the association between darolutamide and docetaxel exposure and the temporal changes in absolute neutrophil count, AST, ALT, total bilirubin, haemoglobin, and selected treatment emergent adverse events (TEAEs) with an overall event rate greater than 10% in the data of Study 17777.

Data and methods

Nonlinear mixed-effects modelling using NONMEM software version 7.4.3 was used, following a visual inspection of the data. The starting point for the development of the base model for each PD safety variable was a turnover type model and different models were considered if deemed necessary. Covariates were investigated using the forward inclusion ($\Delta OFV \leq 6.67$, $p < 0.01$, 1 degree of freedom) and backward elimination procedure ($\Delta OFV > +10.828$, $p > 0.001$, 1 degree of freedom). Model evaluation and qualification was done using generally applied methods.

Results

Different datasets were created. After updating the dataset with additional neutrophil count observations it contained a total of 100852 observations in 1303 patients who received at least one dose of study drug.

The median age of patients was 67 years (range 41-89). In total, 36.5% of patients were aged < 65 years, 46.7% were aged 65-74, 16.3% were aged 75-84 and 0.5% were aged ≥85 at the start of the study. In order to meet the 15% frequency requirement for a covariate category to be investigated in models, the age categories 75-84 and ≥85 were combined into a single ≥75 category. A total of 63.5 % of patients were aged ≥65.

Overall, 15.5% of patients were from mainland China, 11.3% were from Japan, 6.5% were from Korea. 2.8% were from Taiwan, 16.6% were from USA and 47.2% were from the rest of regions. All regions were tested independently despite Japan, Korea and Taiwan not reaching the 15% requirement.

In total, 54.1% of patients had a normal renal function, 36.8% mild, 9.1% moderate, and 0.2% severe renal impairment. To meet the 15% frequency requirement, the categories 'mild', 'moderate' and 'severe' were combined into a single 'mild or worse' category for covariate testing. In total, 92.2% of patients had a normal hepatic function, 7.6% mild and 0.2% moderate hepatic impairment.

Bone metastases were found in 79.7% of patients, 17.3% had visceral metastases and 3% had non-regional lymph node metastases only. To meet the 15% frequency requirement, the visceral metastases and non-regional lymph node metastases only categories were combined into a single category. Overall, 71.8% of patients had ECOG=0 and 28.2% had ECOG=1.

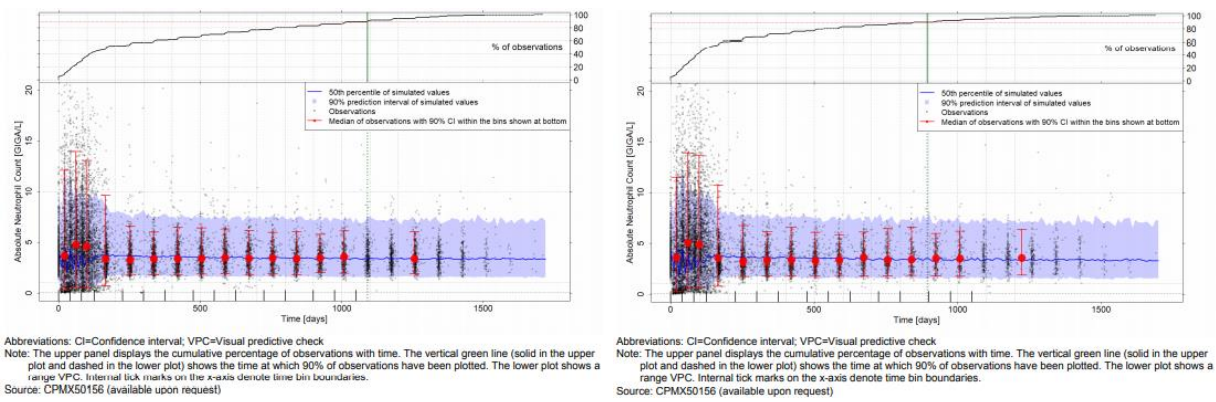
- Absolute neutrophil count

In total, 21208 absolute neutrophil counts from 1303 patients were analysed.The final model is a five-compartment model with three transit compartments and contains the neutrophil production as well as a feedback loop from blood concentration. The effect of docetaxel on neutrophil production is also reflected in the model by each a zero- and first order constant. Neutrophil suppression was found to be different between patients depending on geographical regions (China, USA, Japan, and Korea).

Table 16: Parameter estimates of the final PD for absolute neutrophil counts, study 17777 ARASENS

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
BLN_{pop}	GIGA/L	4.06	0.213	4.04	4.08	Population value for baseline neutrophil count value
MTT_{pop}	day	4.39	0.0845	4.39	4.40	Population value of mean transit time for patients not from mainland China
$SLOPE_{pop}$	L/µg	0.0118	1.84	0.0114	0.0122	Population value of constant describing drop in neutrophil count in relation to docetaxel concentration for patients not from USA
γ		0.239	0.105	0.238	0.239	Constant used in the feedback mechanism relating neutrophils in the blood stream to the proliferation rate
α_{MAX}		-0.202	6.72	-0.229	-0.176	Constant giving the maximal change in neutrophils baseline over time
α_{T50}	day	272	10.5	216	328	Time at which half the maximal change in the baseline neutrophil level occurs
λ		-0.676	0.700	-0.686	-0.667	Rate constant used for box-cox transformation of etas for individuals SLOPE
θ_{CHN}		-0.187	7.11	-0.213	-0.161	Constant describing the change in MTT_{pop} for patients from mainland China
θ_{USA}		0.360	26.7	0.171	0.549	Constant describing the change in $SLOPE_{pop}$ for patients from USA
$\theta_{JPN,MTT}$		-0.196	9.59	-0.233	-0.159	Constant describing the change in MTT_{pop} for patients from Japan
θ_{KOR}		0.420	29.1	0.181	0.660	Constant describing the change in $SLOPE_{pop}$ for patients from Korea
Random effects: Inter-individual variability (OMEGA)						
BLN_{pop} (ω^2)	-	0.0857	6.57	0.0747	0.0968	Inter-individual variability on BLN
BLN_{pop} $(CV)^2$	%	29.9		27.8	31.9	
BLN_{pop} $(Sh)^3$	%	9.25				
MTT_{pop} (ω^2)	-	0.0299	11.8	0.0230	0.0369	Inter-individual variability on MTT
MTT_{pop} $(CV)^2$	%	17.4		15.2	19.4	
MTT_{pop} $(Sh)^3$	%	20.9				
$SLOPE_{pop}$ (ω^2)	-	0.809	4.68	0.734	0.883	Inter-individual variability on SLOPE
$SLOPE_{pop}$ $(CV)^2$	%	112		104	119	
$SLOPE_{pop}$ $(Sh)^3$	%	22.8				
Residual error (SIGMA)						
σ^2	-	0.251	0.814	0.211	0.218	Proportional residual error
CV^4	%	48.9		48.5	49.4	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
[2] The coefficient of variation (CV) is calculated as 100·SQRT(EXP(OMEGA^2)-1)
[3] Shrinkage (Sh) calculated as 100·(1-standard deviation of individual eta estimates/ω)
[4] Both the observations and the model predictions were log-transformed and an additive residual error model was used. This is equivalent to an exponential residual error model on untransformed data and the coefficient of variation (CV) calculated as 100·SQRT(EXP(σ^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of σ^5.



Abbreviations: CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Abbreviations: CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Figure 7: VPC of neutrophils final model for darolutamide (left) and placebo (right) treated patients of Study 17777

Slight differences due to region or race were established. The proportion of patients with neutropenia grade 3 and grade 4 based on the region or race, stratified by treatment arm are shown in Table 17. Higher incidences were reported in patients from the Asia Pacific region compared with patients from North America and rest of the world (ROW) in both treatment arms. These observed differences in Grade 3 or 4 neutrophil count decreased among geographical regions were generally consistent with the assessment of the typical patient's profile of absolute neutrophil count predicted by the PK-PD model, and are generally consistent in both treatment arms.

Table 17: Grade 3 and 4 TEAEs of neutrophil count decreased and neutropenia by geographical region and treatment arm (SAF)

		Darolutamide+docetaxel arm Geographical region			Placebo+docetaxel arm Geographical region		
MedDRA (v.24.1) PT	Worst CTCAE grade	North America N=125 n (%)	Asia Pacific N=230 n (%)	ROW N=297 n (%)	North America N=117 n (%)	Asia Pacific N=242 n (%)	ROW N=291 n (%)
Neutrophil count decreased	Any-grade	23 (18.4)	126 (54.8)	21 (7.1)	16 (13.7)	126 (52.1)	13 (4.5)
	Grade 3	7 (5.6)	26 (11.3)	6 (2.0)	8 (6.8)	28 (11.6)	5 (1.7)
	Grade 4	14 (11.2)	89 (38.7)	9 (3.0)	4 (3.4)	90 (37.2)	5 (1.7)
Neutropenia	Any-grade	13 (10.4)	16 (7.0)	39 (13.1)	17 (14.5)	22 (9.1)	37 (12.7)
	Grade 3	2 (1.6)	2 (0.9)	14 (4.7)	4 (3.4)	2 (0.8)	12 (4.1)
	Grade 4	8 (6.4)	12 (5.2)	18 (6.1)	11 (9.4)	19 (7.9)	20 (6.9)

Abbreviations: 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; PT=Preferred term; ROW=Rest of the World; SAF=Safety analysis set; v.=Version

Notes: Any adverse events with missing CTCAE grade are not included in this summary table.
CTCAE version 4.03.

- Aspartate aminotransferase (AST)

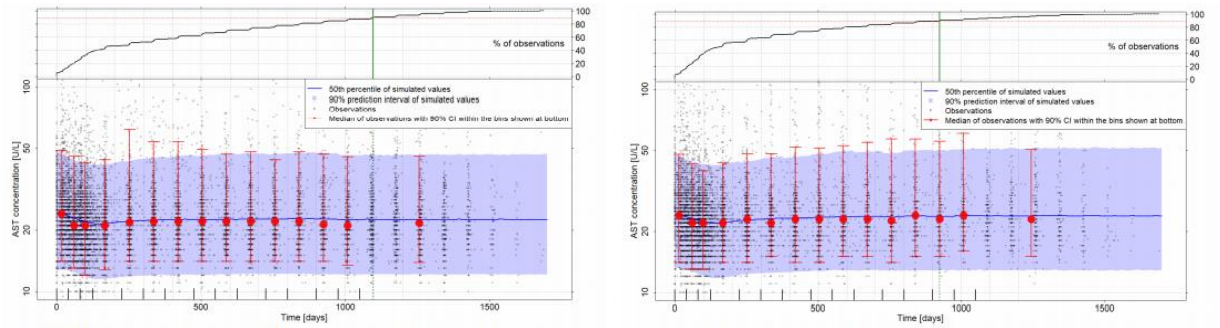
Overall, 19384 AST concentrations from 1303 patients were analysed. The final model structure was a turnover model.

Parameter of the final model estimates are listed in Table 18.The typical percentage change in AST across all patients is shown in Table 19. AST concentration was found to be reduced during docetaxel treatment in both study arms. No other patient characteristics were found to influence AST. Differences in docetaxel exposure were not found to AST. No differences between darolutamide and control patients were identified.

Table 18: Parameter estimates of the final PD model for AST, study 17777 ARASENS

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
α	U/L	24.9	1.32	24.2	25.5	Factor of production rate
K_{out}	1/day	0.00593	12.5	0.00448	0.00738	Elimination rate constant for patient not receiving docetaxel treatment
BLN	U/L	24.2	1.01	23.8	24.7	Population baseline value of ALT concentration
θ_{DTX}		0.212	12.4	0.161	0.264	Docetaxel treatment effect on K_{out}
Random effects: Inter-individual variability (OMEGA)						
K_{out} (ω^2)	-	0.159	8.52	0.132	0.185	Inter-individual variability on K_{out}
K_{out} (CV)[1]	%	41.5		37.6	45.1	
K_{out} (Sh)[2]	%	8.19				
BLN (ω^2)	-	0.105	5.83	0.0926	0.117	Inter-individual variability on BLN
BLN (CV)[1]	%	33.2		31.1	35.2	
BLN (Sh)[2]	%	10.26				
Residual error (SIGMA)						
(σ^2)	-	0.0805	5.26	0.0722	0.0888	Additive residual error on log scale
(CV)[3]	%	8.87		8.40	9.31	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
[1] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[2] Shrinkage (Sh) calculated as 100·(1-standard deviation of individual eta estimates/ω)
[3] The coefficient of variation (CV) is calculated as 100·SQRT(σ2)/3.2 which is the CV for an observation of 3.2 on log scale, which corresponds to an AST concentration of 25 U/L.



Abbreviations: AST=Aspartate aminotransferase; CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Figure 8: VPC of AST final model for darolutamide (left) and placebo (right) treated patients of Study 17777

Table 19: Typical percentage change of AST concentration for all patients, study 17777 ARASENS

Typical patient	Treatment arm	Week 9 % change [1]	Week 18 % change [1]	Week 52 % change [1]	Week 104 % change [1]
All patients	Darolutamide	-5.50 (-6.71, -4.43)	-9.01 (-10.9, -7.23)	-0.269 (-2.55, 2.02)	2.25 (-0.381, 4.86)
	Control	-5.47 (-6.63, -4.38)	-9.01 (-10.7, -7.2)	-0.184 (-2.48, 2.01)	2.39 (-0.151, 4.95)

[1] Percentage change from baseline: median (lower bound of 90% CI, upper bound of 90% CI)

- Alanine aminotransferase (ALT)

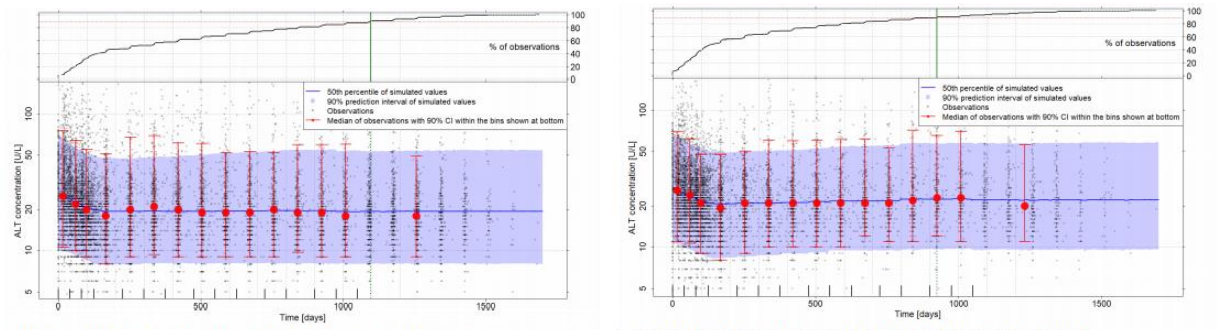
Overall, 19606 ALT concentrations from 1303 patients were analysed. The final model was a turnover model as also used for AST. Parameter estimates are listed in Table 20. Docetaxel, age, Chinese, and

Japanese were identified as statistically significant covariates. The overall model performance showed its ability to describe the time course of ALT on each sub-group of population.

Table 20: Parameter estimates of the final PD model for ALT, study 17777 ARASENS

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
α	U/L	22.1	1.95	21.3	23.0	Constant for production rate
$K_{out,pop}$	1/day	0.00486	9.73	0.00393	0.00578	Population removal rate for a typical patient of age 67 years, from neither Japan nor mainland China and not currently receiving docetaxel treatment
BLN	U/L	26.2	1.53	25.5	27.0	Population baseline value of ALT concentration
θ_{DTX}	-	0.288	15.8	199	377	Proportional effect of docetaxel treatment on removal rate
θ_{AGE}	-	0.00864	23.6	0.00463	0.0126	Effect of continuous age on removal rate
θ_{JAPAN}	-	0.263	21.3	0.153	0.373	Proportional effect of region=Japan on removal rate
θ_{CHINA}	-	0.217	23.5	0.117	0.316	Proportional effect of region=mainland China on removal rate
Residual error (SIGMA)						
(σ^2)	-	0.136	3.93	0.125	0.146	Additive residual error
(CV)[3]	%	12.3		11.8	12.7	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
[1] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[2] Shrinkage (Sh) calculated as 100·(1-standard deviation of individual ETA estimates/ω)
[3] The coefficient of variation (CV) is calculated as 100·SQRT(σ2)/3.0 which is the CV for an observation of 3.0 on log scale, which corresponds to an ALT concentration of 20 U/L.



Abbreviations: ALT=Alanine aminotransferase; CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Figure 9: VPC of ALT final model for darolutamide (left) and placebo (right) treated patients of Study 17777

The typical percentage change in ALT across all patients is shown in Table 21. ALT concentration was found to be reduced during docetaxel treatment in both study arms. Older patients and patients from Japan or mainland China were associated with decreasing ALT levels. Differences in docetaxel exposure were not found to ALT. No differences between darolutamide and control patients were identified.

Table 21: Typical percentage change of ALT concentration, study 17777 ARASENS

Typical patient	Treatment arm	Week 9 % change[1]	Week 18 % change[1]	Week 52 % change[1]	Week 104 % change[1]
All patients	Darolutamide	-12.2 (-20.9, -7.72)	-20.2 (-33.1, -13.1)	-18.7 (-36.1, -7.8)	-18.2 (-36.9, -5.57)
	Control	-12.1 (-20.8, -7.47)	-20.2 (-33.2, -12.7)	-18.7 (-35.9, -7.94)	-18.1 (-36.7, -5.9)
Age ≥ 65 years	Darolutamide	-13.1 (-21.7, -10.3)	-21.7 (-34.3, -17.2)	-20.7 (-37.7, -14.8)	-20.5 (-38.7, -13.7)
	Control	-13.1 (-21.7, -10.1)	-21.6 (-34.3, -16.9)	-20.8 (-37.4, -14.6)	-20.5 (-38.1, -13.5)
Age < 65 years	Darolutamide	-9.60 (-17.8, -6.53)	-16.3 (-28.8, -11.2)	-12.7 (-30.4, -5.37)	-11.5 (-31.0, -2.51)
	Control	-9.70 (-17.4, -6.47)	-16.4 (-28.2, -11.1)	-13.0 (-29.7, -5.37)	-11.6 (-30.3, -2.45)
Region: mainland China	Darolutamide	-18.7 (-22.8, -14.1)	-30.1 (-35.8, -23.2)	-32.4 (-39.2, -23.6)	-33.0 (-40.2, -23.7)
	Control	-18.8 (-23.1, -13.6)	-30.3 (-36.1, -22.5)	-32.6 (-39.5, -22.7)	-33.2 (-40.1, -22.6)
Region: Japan	Darolutamide	-19.0 (-22.8, -14.3)	-30.5 (-36.0, -23.6)	-33.0 (-39.3, -24.1)	-33.7 (-40.2, -24.1)
	Control	-18.3 (-22.5, -13.9)	-29.6 (-35.3, -23.0)	-31.7 (-38.7, -23.4)	-32.3 (-39.5, -23.4)

[1] Percentage change from baseline: median (lower bound of 90% CI, upper bound of 90% CI)

- Total bilirubin

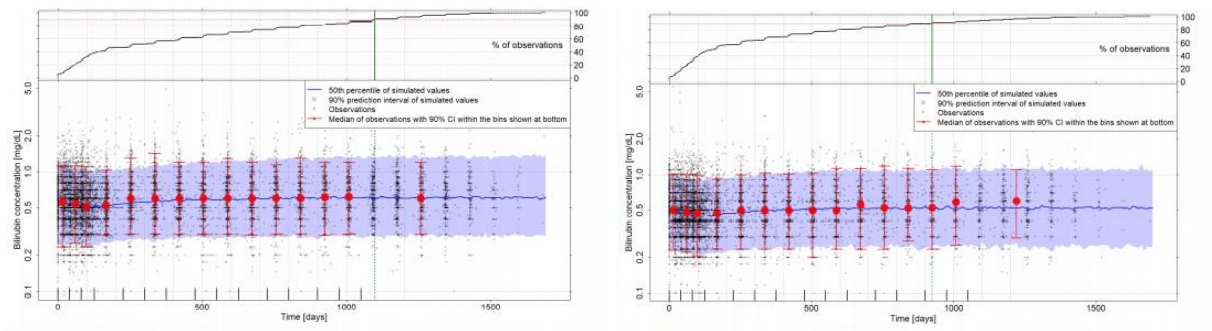
Overall, 19337 bilirubin observations from 1303 patients were analysed. The final model was a turnover model.

Parameter estimates of the final model are listed in Table 22. Docetaxel, darolutamide, age, Chinese, Japanese, and Korean were identified as statistically significant covariates. The overall model performance demonstrates its ability to describe the time course of bilirubin on each sub-group of population.

Table 22: Parameter estimates of the final PD model for total bilirubin, study 17777 ARASENS

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
BLN_{pop}	mg/dL	0.541	1.51	0.525	0.557	Population value for baseline concentration of bilirubin
$K_{outND,pop}$	day^{-1}	0.00596	3.26	0.00558	0.00634	Population value for the rate of decrease in bilirubin concentration without the effect of docetaxel
K_{in}	day^{-1}	0.00282	2.68	0.00267	0.00297	Value for the rate of increase in bilirubin concentration
θ_{DTX}		0.825	3.37	0.770	0.879	Proportion of recorded docetaxel treatment period in which an effect in the value of K_{out} is seen
θ_{DTXEFF}		0.368	4.22	0.337	0.398	Change in K_{out} due to the use of docetaxel
λ		-0.800	7.82	-0.922	-0.677	Rate constant used for box-cox transformation of etas for K_{outND}
θ_{DARO}		-0.143	12.1	-0.177	-0.109	Effect of taking darolutamide on K_{outND}
θ_{AGE}		-0.00505	26.0	-0.00762	-0.00247	Effect of the patient's age at baseline on K_{outND}
θ_{CHINA}		-0.221	10.9	-0.269	-0.174	Effect of region=mainland China on K_{outND}
θ_{KOREA}		-0.257	15.0	-0.332	-0.181	Effect of region=Korea on K_{outND}
θ_{JAPAN}		-0.193	14.6	-0.248	-0.138	Effect of region=Japan on K_{outND}
Random effects: Inter-individual variability (OMEGA)						
BLN_{pop} (ω^2)	-	0.170	302	0.159	0.180	Inter-individual variability on BLN
BLN_{pop} (CV)[1]	%	43.0		41.5	44.5	
BLN_{pop} (Sh)[2]	%	4.75				
$K_{outND,pop}$ (ω^2)	-	0.146	5.21	0.131	0.161	Inter-individual variability on K_{outND}
$K_{outND,pop}$ (CV)[1]	%	39.7		37.5	41.8	
$K_{outND,pop}$ (Sh)[2]	%	8.01				
Residual error (SIGMA)						
σ^2	-	0.0657	0.595	0.0650	0.0665	Proportional residual error
CV[3]	%	25.6		25.5	25.8	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
[1] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[2] Shrinkage (Sh) calculated as 100·(1-standard deviation of individual eta estimates/ω)
[3] Coefficient of variation (CV) calculated as 100·SQRT(σ^2). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2.



Abbreviations: CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Figure 10: VPC of bilirubin final model for darolutamide (left) and placebo (right) treated patients of Study 17777

The typical percentage change in AST across all patients is shown in Table 23. Total bilirubin was found to be reduced during docetaxel treatment in both study arms. Older patients and patients from Japan, Korea or mainland China were associated with increased total bilirubin. Darolutamide treatment was found to be associated with increased bilirubin levels over control, with model-predicted 0.1% (90% CI -8.6 to 24.7) increase from baseline after one year of treatment for a typical darolutamide-treated patient versus -12.1% (90% CI - 19.9 to 10.3) reduction from baseline for a typical control patient. The association with darolutamide treatment was consistent across the darolutamide exposure range at 600 mg BID.

Table 23: Typical percentage change of total bilirubin, study 17777 ARASENS

Typical patient	Treatment arm	Week 9 % change[1]	Week 18 % change[1]	Week 52 % change[1]	Week 104 % change[1]
All patients	Darolutamide	-8.19 (-11.9, 0.563)	-10.1 (-15.7, 3.83)	0.0829 (-8.63, 24.7)	3.84 (-6.39, 35.3)
	Control	-13.5 (-17.2, -4.17)	-18.1 (-23.7, -3.97)	-12.1 (-19.9, 10.3)	-10.2 (-19.0, 16.7)
Age ≥ 65 years	Darolutamide	-7.26 (-10.1, 0.922)	-8.91 (-13.0, 4.54)	2.38 (-4.55, 25.9)	6.63 (-1.61, 37.2)
	Control	-12.5 (-15.5, -3.84)	-16.7 (-21.0, -3.29)	-9.93 (-16.5, 11.7)	-7.78 (-15.3, 18.4)
Age < 65 years	Darolutamide	-9.68 (-12.8, -0.611)	-12.5 (-17.1, 1.94)	-3.52 (-10.7, 21.2)	-0.435 (-8.72, 31)
	Control	-15.3 (-18.2, -5.70)	-20.7 (-25.0, -6.39)	-15.8 (-22.0, 6.43)	-14.4 (-21.2, 11.6)
Region: mainland China	Darolutamide	-1.36 (-3.68, 1.07)	0.831 (-2.95, 4.77)	19.0 (12.3, 26.4)	27.8 (18.9, 37.7)
	Control	-5.93 (-8.80, -2.92)	-6.63 (-11.1, -1.79)	5.99 (-1.37, 14.2)	11.1 (2.12, 21.2)
Region:Japan	Darolutamide	-1.53 (-4.42, 0.842)	0.359 (-4.22, 4.41)	18.3 (9.98, 25.8)	26.9 (16.1, 36.9)
	Control	-6.55 (-9.51, -3.94)	-7.49 (-12.3, -3.45)	4.41 (-3.22, 11.5)	9.08 (-0.0622, 17.9)
Region: Korea	Darolutamide	0.0583 (-3.28, 3.18)	3.09 (-2.59, 8.28)	23.3 (13.0, 33.4)	33.6 (19.9, 47.7)
	Control	-4.34 (-8.17, -1.10)	-4.05 (-10.0, 1.09)	10.3 (0.376, 19.7)	16.5 (4.30, 28.9)

[1] Percentage change from baseline: median (lower bound of 90% CI, upper bound of 90% CI)

- Haemoglobin

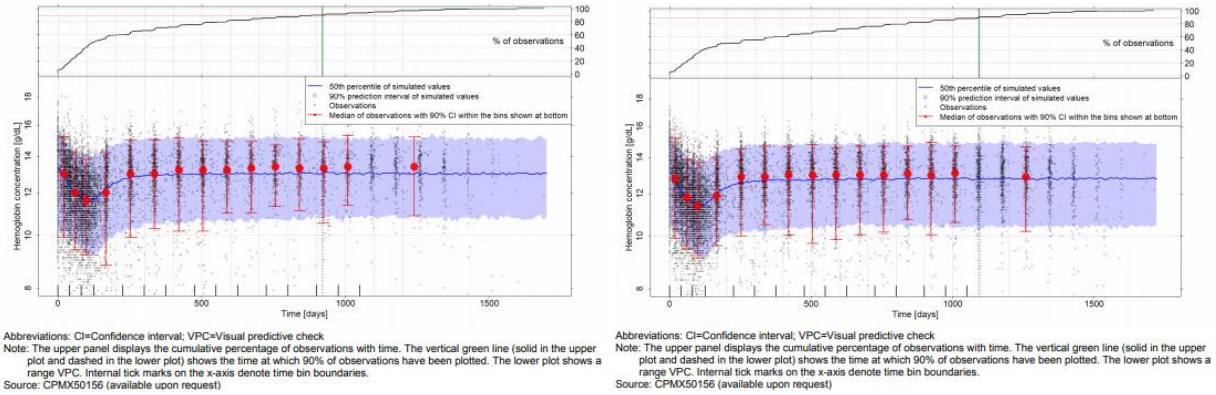
Overall, 21317 haemoglobin observations from 1303 patients were analysed. The final model was a turnover model.

Parameter estimates of the final model are listed in Table 22. Docetaxel, darolutamide, prednisolone, age, Chinese, Japanese, and Korean were identified as statistically significant covariates. The overall model performance showed its ability to describe the time course of haemoglobin on each sub-group of population.

Table 24: Parameter estimates of the final PD model for haemoglobin, study 17777 ARASENS

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
BLN_{pop}	g/dL	13.3	0.405	13.2	13.4	Population value for baseline concentration of hemoglobin
K_{outND}	day^{-1}	0.0207	2.55	0.0197	0.0222	Population value for the rate of decrease in hemoglobin concentration without the effect of docetaxel
$K_{in,pop}$		13.0	0.445	12.9	13.1	Multiplicative constant used to give the population value of K_{in} in terms of K_{outND}
θ_{DTX}		0.933	0.438	0.925	0.941	Proportion of docetaxel treatment period in which an effect in the value on the turnover parameters is seen
θ_{KO}		1.40	3.66	1.30	1.50	Constant used in describing the change in K_{out} due to the use of docetaxel
θ_{KI}		0.892	0.575	0.882	0.902	Constant used in describing the change in K_{in} due to the use of docetaxel
λ		-3.34	5.06	-3.67	-3.01	Rate constant used for box-cox transformation of etas for individuals baseline and K_{outND}
θ_{AGE1}		-0.00235	13.3	-0.00296	-0.00174	Parameter describing the influence of age on $K_{in,pop}$
θ_{AGE2}		0.00156	26.2	0.000759	0.00236	Parameter describing the influence of age on θ_{KO}
θ_{PREDN}		-0.0259	22.9	-0.0376	-0.0143	Parameter describing the influence of a patient taking prednisone/prednisolone during the docetaxel treatment period on θ_{KO}
θ_{DARO}		-0.0197	24.2	-0.0290	-0.0103	Parameter describing the influence of a patient being treated with darolutamide on $K_{in,pop}$
θ_{DTXA1}		-0.278	12.4	-0.345	-0.210	Parameter describing the influence of the patients total docetaxel AUC on θ_{KO}
θ_{DTXA2}		1.03	2.22	0.981	1.07	Parameter describing the influence of the patient's total docetaxel AUC, along with θ_{DTXA1}, on θ_{KI}
θ_{JAPAN}		0.0675	15.0	0.0476	0.0874	Parameter describing the influence of region=Japan on KoutC
θ_{CHINA}		-0.0449	19.3	-0.0618	-0.0279	Parameter describing the influence of region=mainland China on KinC
θ_{KOREA}		-0.0431	27.2	-0.0660	-0.0201	Parameter describing the influence of region=Korea on KinND
Random effects: Inter-individual variability (OMEGA)						
BLN_{pop} (ω^2)	-	0.0121	5.91	0.0107	0.0135	Inter-individual variability on BLN
BLN_{pop} (CV)[1]	%	11.0		10.4	11.6	
BLN_{pop} (Sh)[2]	%	10.41				
K_{inND} (ω^2)	-	0.00874	4.84	0.00791	0.00957	Inter-individual variability on K_{inND}
K_{inND} (CV)[1]	%	9.37		8.91	9.81	
K_{inND} (Sh)[2]	%	5.19				
K_{outC} (ω^2)	-	0.00801	4.55	0.00730	000873	Inter-individual variability on K_{outC}
K_{outC} (CV)[1]	%	8.97		8.56	9.36	
K_{outC} (Sh)[2]	%	12.56				
Residual error (SIGMA)						
(σ^2)	-	0.00376	0.279	0.00374	0.00378	Proportional residual error
CV[3]	%	6.13		6.11	6.15	

LLCI = lower limit of 95% confidence interval (estimate – 1.96·SE)
ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
RSE = relative standard error (100·SE/estimate)
[1] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2
[2] Shrinkage (Sh) calculated as 100·(1-standard deviation of individual eta estimates/ω)
[3] Coefficient of variation (CV) calculated as 100·SQRT(σ^2).



Abbreviations: CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Abbreviations: CI=Confidence interval; VPC=Visual predictive check
Note: The upper panel displays the cumulative percentage of observations with time. The vertical green line (solid in the upper plot and dashed in the lower plot) shows the time at which 90% of observations have been plotted. The lower plot shows a range VPC. Internal tick marks on the x-axis denote time bin boundaries.
Source: CPMX50156 (available upon request)

Figure 11: VPC of hemoglobin final model for darolutamide (left) and placebo (right) treated patients of Study 17777

Haemoglobin was found to be reduced during docetaxel treatment in both study arms. The reduction in haemoglobin due to docetaxel treatment was more pronounced in those with higher docetaxel exposure, older patients, patients from Japan and patients from China. After haemoglobin levels recovered from docetaxel treatment, darolutamide treated patients continued to be associated with lower haemoglobin levels than control patients for the remainder of the study, although the model-predicted difference is small with a -4.5% (90% CI - 8.1 to 1.0) reduction from baseline one year after treatment start for a typical darolutamide-treated patient versus -2.4% (90% CI -5.9 to 0.77) reduction from baseline for a typical control patient). The same applies for older versus younger patients and patients from Korea versus not from Korea.

For patients from Japan, on average, 1.56-fold higher exposure in these patients did not result in a different change in haemoglobin over time compared with patients from the rest of the regions. The predicted change in haemoglobin after 1 year in the darolutamide + docetaxel arm was −5.6% (90% CI: [−7.9%; −2.2%]) in a typical Japanese patient vs. −4.3% (90% CI: [−7.3%; −0.7%]) in a typical rest of the regions patient and a comparable difference between a Japanese vs. rest of the regions patient was observed in the placebo + docetaxel arm, i.e., −3.3% (90% CI: [−6%; −0.1%]) vs. −2.4% (90% CI: [−5.4%; +1.1%], respectively. Similarly, the 1.27-fold higher exposure in patients from mainland China vs. rest of the regions was not associated with differences in haemoglobin decrease. While the predicted change in haemoglobin after 1 year was −4.4% (90% CI: [−6.8%, −1.6%) in a typical patient from mainland China vs. −4.3% (90% CI: [−7.3%; −0.7%]) in a typical rest of the regions patient, a comparable difference between a patient from mainland China vs. a rest of the regions patient was observed in the placebo + docetaxel arm, i.e., −2.4% (90% CI: [−5.1%, +1.2%]) vs. −2.4% (90% CI: [−5.4%; +1.1%], respectively.

Table 25: Typical percentage change of haemoglobin, study 17777 ARASENS

Typical patient	Treatment arm	Week 9 % change[1]	Week 18 % change[1]	Week 52 % change[1]	Week 104 % change[1]
All patients	Darolutamide	-11.9 (-18.0, -7.17)	-12.7 (-18.5, -7.57)	-4.53 (-8.08, -0.991)	-4.47 (-8.01, -0.948)
	Control	-10.6 (-16.5, -5.74)	-11.0 (-17.1, -5.67)	-2.43 (-5.87, 0.766)	-2.37 (-5.80, 0.827)
Age ≥ 65 years	Darolutamide	-13.3 (-19.0, -9.81)	-14.1 (-19.4, -10.5)	-5.29 (-8.49, -3.56)	-5.23 (-8.42, -3.49)
	Control	-12.2 (-17.2, -8.27)	-12.9 (-17.5, -8.7)	-3.44 (-6.92, -1.54)	-3.38 (-6.86, -1.47)
Age < 65 years	Darolutamide	-9.47 (-14.2, -5.9)	-9.89 (-14.5, -5.98)	-2.67 (-6.12, 0.114)	-2.61 (-6.06, 0.177)
	Control	-8.38 (-12.9, -4.73)	-8.49 (-12.9, -4.72)	-0.725 (-2.86, 1.72)	-0.667 (-2.81, 1.77)
Prednisone or prednisolone	Darolutamide	-10.9 (-16.6, -6.48)	-11.7 (-17.5, -6.84)	-4.43 (-7.42, -1.42)	-4.37 (-7.37, -1.37)
	Control	-9.53 (-15.2, -4.92)	-9.98 (-15.6, -4.87)	-2.48 (-5.68, 0.826)	-2.43 (-5.62, 0.874)
No Prednisone or prednisolone	Darolutamide	-12.8 (-19.1, -8.24)	-13.6 (-19.5, -8.49)	-4.77 (-8.84, -1.07)	-4.70 (-8.79, -1.00)
	Control	-11.4 (-17.3, -6.40)	-11.9 (-17.6, -6.36)	-2.67 (-6.63, 1.16)	-2.59 (-6.56, 1.21)
Docetaxel AUC_{Total} > 28381 h·µg/L	Darolutamide	-11.7 (-16.4, -6.97)	-12.8 (-17.9, -7.43)	-4.79 (-7.79, -1.06)	-4.72 (-7.74, -1.01)
	Control	-10.2 (-15.3, -5.20)	-11.0 (-16.5, -5.34)	-2.69 (-6.14, 1.23)	-2.61 (-6.07, 1.30)
Docetaxel AUC_{Total} ≤ 28381 h·µg/L	Darolutamide	-12.6 (-19.2, -6.83)	-12.9 (-19.3, -6.88)	-4.32 (-8.41, -0.906)	-4.25 (-8.33, -0.854)
	Control	-11.4 (-17.7, -6.06)	-11.4 (-17.6, -5.89)	-2.38 (-5.95, 0.871)	-2.32 (-5.87, 0.929)
Region: Japan	Darolutamide	-17.8 (-21.4, -13.3)	-18.1 (-21.6, -13.7)	-5.49 (-8.22, -2.17)	-5.40 (-8.11, -2.09)
	Control	-15.6 (-19.2, -11.5)	-15.7 (-19.1, -11.3)	-3.12 (-5.56, -0.141)	-3.03 (-5.48, -0.0545)
Region: mainland China	Darolutamide	-14.0 (-17.2, -10.7)	-14.5 (-18.1, -10.9)	-4.34 (-6.86, -1.52)	-4.26 (-6.79, -1.43)
	Control	-13.0 (-16.1, -8.70)	-13.2 (-16.6, -8.49)	-2.47 (-5.06, 0.899)	-2.39 (-4.99, 0.951)
Region: Korea	Darolutamide	-14.7 (-18.5, -10.3)	-15.8 (-19.8, -11.2)	-8.36 (-11.6, -4.72)	-8.30 (-11.6, -4.66)
	Control	-13.5 (-17.2, -9.16)	-14.6 (-18.3, -9.66)	-6.77 (-9.91, -2.95)	-6.71 (-9.84, -2.90)

[1] Percentage change from baseline: median (lower bound of 90% CI, upper bound of 90% CI)

2.3.4. Discussion on clinical pharmacology

- *Population PK modelling darolutamide*

Although some slight misspecifications in the pc-VPC were identified for (S,R)-darolutamide, overall, the population PK model is considered fit-for-purpose to inform on PK characteristics and exposure-response relationships.

- *Comparison of studies 17777 ARASENS and 17712 ARAMIS*

Based on PK analyses systemic exposure was shown to be generally lower and the PK more variable in patients with mHSPC in study ARASENS compared to patients with nmCRPC in study ARAMIS. However, this difference does not appear to be attributed to the cancer type but to other patient characteristics (e.g. age, body weight). Therefore, the PK of darolutamide is considered to be generally comparable between mHSPC and nmCRPC patients. Available data from study 17777 ARASENS suggested a higher increase in exposure ($AUC_{(0-12)ss}$) for Japanese patients (mean ratio compared to rest of regions = 1.56 (90%CI: 1.43 – 1.70) as compared to the previous analysis of data from study 17712 ARAMIS (mean ratio compared to rest of regions =1.42 (90%CI: 1.33 - 1.53)). See section 5.2 of the SmPC.

- *Population PK modelling of docetaxel and effect of darolutamide on PK of docetaxel*

Based on the presented results, darolutamide 600 mg BID orally administered resulted in no clinically relevant changes in the systemic exposure of docetaxel (75 mg/mg^2 as 1 hour IV infusion every 21 days) in mHSPC patients.

- *PK/PD modelling for efficacy and safety*

Modelling aspects

Several PK/PD models have been developed to characterise the time course of darolutamide, docetaxel, PSA, neutrophil count, ALT, ALT, bilirubin and haemoglobin.

Although adequate PK data were limited, the current analysis reveals the ability of the model to capture the time-course of PSA over time and relevant covariates to explain differences among groups. No clear relationship between darolutamide exposure and PSA response was identified.

Exploratory analysis suggested no differences in time-course of total testosterone between darolutamide-treated and control patients.

Regarding neutrophil count, ALT, AST, bilirubin, and haemoglobin, no relevant differences on model performance was observed across the different treatment arms (refer to VPCs), suggesting that the model adequately captures the pharmacodynamic endpoints (neutrophil count, ALT, AST, bilirubin, and haemoglobin) on each arm.

The justification of including an alpha parameter, which represents the fraction of the correlation between Kin or Kout in the AST and ALT model is not completely understood, although it seems to improve the prediction of the AST and ALT time-course data. The sparse data available and the identification of three parameters of the turn-over model may be explained by non-steady state conditions of patients before initiating treatment or no relevant information of baseline AST and ALT values collected. Therefore, the estimation of baseline of AST and ALT together with Kin and Kout is supported to address the non-steady-state conditions of patients.

The Applicant recognized the inability to incorporate longitudinal predicted concentrations of docetaxel to predict AST, ALT, and bilirubin profiles over time. Although the PK/PD model captures the observed data, no relevant information is incorporated to understand how changes in docetaxel exposure may affect the response time-course. Therefore, simulation-based analyses to support changes in docetaxel dose level or schedule are of limited information.

Neutrophil count, ALT, ALT, bilirubin and haemoglobin

Differences in neutrophil suppression due to docetaxel treatment in both study arms were identified for patients in different geographical regions (China, USA, Japan, and Korea). A slightly higher incidence of neutropenia Grade 3 / 4 in the placebo + docetaxel arm was observed versus the darolutamide + docetaxel arm.

AST and ALT concentrations were reduced during docetaxel treatment in both study arms. Older patients and patients from Japan or mainland China were associated with decreasing ALT levels. Differences in docetaxel exposure were not associated with changes in ALT levels. Overall, no differences between darolutamide and control patients were identified for AST and ALT.

Total bilirubin was reduced during docetaxel treatment in both study arms. Older patients and patients from Japan, Korea or mainland China were associated with increased total bilirubin. Darolutamide treatment was associated with increased bilirubin levels consistent across the darolutamide exposure range at 600 mg BID.

The co-administration of darolutamide with docetaxel was shown to reduce the decrease on bilirubin (BIL) level compared to docetaxel only. Although no definitive conclusions could be established regarding the mechanism involved in bilirubin change after darolutamide, it has been hypothesized that the inhibition of OATP1B1 and OATP1B3 by darolutamide may play a role, leading to higher BIL levels.

Haemoglobin was reduced during docetaxel treatment in both study arms. The reduction in haemoglobin due to docetaxel treatment was more pronounced in those with higher docetaxel exposure, older patients, patients from Japan and patients from China. Darolutamide treatment was also associated with reduced haemoglobin levels.

2.3.5. Conclusions on clinical pharmacology

The PK of darolutamide appear generally comparable between mHSPC and nmCRPC patients.

Overall, the adequacy of the current PK/PD model to describe the observed (response) data is supported. However, it should be highlighted that the current PK/PD models developed for each PD outcome did not take into account how changes in darolutamide or docetaxel exposure may affect the PD outcome. Therefore, although several covariates were statistically identified to explain differences in PD response over time, the PK/PD models were not suitable to support any dose schedule modification since it is not possible to estimate how differences in exposure may translate into the PD outcome.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The selected dose of darolutamide in ARASENS study is 600 mg bd tablets which is the same as the selected dose for the currently approved indication in the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

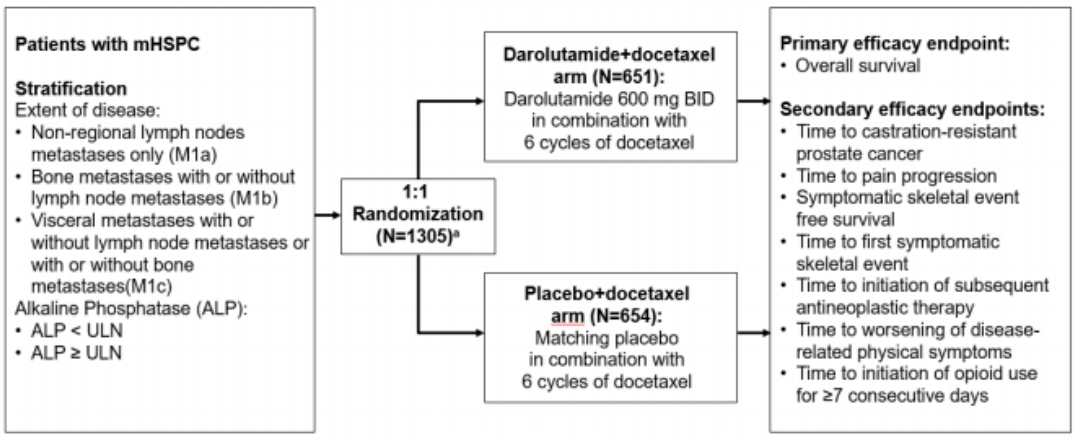
The 600 mg bd dose of tablet formulation for treatment of patients with mHSPC in combination with docetaxel was primarily supported by a popPK meta-analysis and data of Study 17777.

2.4.2. Main study(ies)

Study ARASENS

Study ARASENS is a randomized, double–blind, placebo–controlled Phase III study of darolutamide (ODM–201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone–sensitive prostate cancer.

Methods



Abbreviations: ADT=Androgen deprivation therapy; ALP=Alkaline phosphatase; BID=twice daily; GCP=Good Clinical Practice; mHSPC=Metastatic hormone-sensitive prostate cancer; ULN=Upper limit of normal.
a: 1306 patients were randomized. 1 patient was excluded due to GCP violation.
Patients in both treatment arms received ADT throughout the study.

Figure 12: ARASENS Study Design

Study participants

Key inclusion criteria included:

- Written informed consent

- Males ≥18 years of age

- Histologically or cytologically confirmed adenocarcinoma of prostate

- Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, either by contrast–enhanced abdominal/pelvic/chest computed tomography (CT) or magnetic resonance imaging (MRI) scan assessed by investigator and confirmed by central radiology review. Metastatic disease is defined as either malignant lesions in bone scan or measurable lymph nodes above the aortic bifurcation or soft tissue/visceral lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Lymph nodes are measurable if the short axis diameter is ≥15 mm, soft tissue/visceral lesions are measurable if the long axis diameter is ≥10 mm. Patients with regional lymph node metastases only (N1, below the aortic bifurcation) will not be eligible for the study. Only patients with non–regional lymph node metastases (M1a) and/or bone metastases (M1b) and/or other sites of metastases with or without bone disease (M1c) will be eligible.

- Patients must be candidates for ADT and docetaxel therapy per investigator's judgment

- Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first generation anti–androgen, but no longer than 12 weeks before randomization. For patients receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 4 weeks, prior to randomization is recommended. First generation anti– androgen had to be stopped prior to randomization.

- An Eastern Cooperative Oncology Group performance status of 0 or 1

- Blood counts at Screening: hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥$1.5x10^9$ /L, platelet count ≥$100x10^9$ /L (patient must not have received any growth factor within 4 weeks or a blood transfusion within 7 days of the hematology laboratory sample obtained at Screening)

- Screening values of serum alanine aminotransferase and/or aspartate transaminase ≤1.5 x upper limit of normal (ULN), total bilirubin ≤ULN, creatinine ≤2.0 x ULN

- Sexually active male patients must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the treatment with darolutamide+placebo and for 3 months after the end of the treatment with darolutamide+placebo and 6 months after treatment with docetaxel

Key exclusion criteria included:

- Prior treatment with:

    o LHRH agonist/antagonists started more than 12 weeks before randomization

    o Second–generation androgen receptor (AR) inhibitors such as enzalutamide, ARN–509, darolutamide, other investigational AR inhibitors

    o Cytochrome P 17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as antineoplastic treatment for prostate cancer

    o Chemotherapy or immunotherapy for prostate cancer prior to randomization

- Treatment with radiotherapy (external beam radiation therapy, brachytherapy, or radiopharmaceuticals) within 2 weeks before randomization

- Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation of the study drugs

- Contraindication to both CT and MRI contrast agent

- Had 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)

- Uncontrolled hypertension as indicated by a resting systolic blood pressure (BP) ≥160 mmHg or diastolic BP ≥100 mmHg despite medical management

- Had a 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 (ie, pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥5 years before randomization and from which the patient has been disease–free

- A gastrointestinal disorder or procedure which is expected to interfere significantly with absorption of study drug

- An active viral hepatitis, known human immunodeficiency virus infection with detectable viral load, or chronic liver disease with a need for treatment

- Previous (within 28 days before the start of study drug or 5 half–lives of the investigational treatment of the previous study, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s)

- Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the patient and/or his/her compliance with study procedures, or may interfere with the patient's participation in the study or evaluation of the study results

- Inability to swallow oral medications

- Close affiliation with the investigational site (eg, a close relative of the investigator, dependent person [eg, employee or student of the investigational site])

- Previous assignment to treatment in this study Study design: Randomized, double–blind, placebo–controlled, multicente

Treatments

Patients were randomised in a 1:1 ratio to the treatments as specified below:

- Darolutamide tablets orally 600 mg [2 x 300 mg tablets] twice daily [bd], tablet formulation combined with docetaxel at a dose of 75 mg/m^2 as an IV infusion every 21 days for 6 cycles, starting within 6 weeks after the start of study drug.
- Placebo tablets orally combined with docetaxel at a dose of 75 mg/m^2 as an IV infusion every 21 days for 6 cycles, starting within 6 weeks after the start of study drug.

Docetaxel could be administered in combination with prednisone/prednisolone at the discretion of the Investigator. To prevent hypersensitivity reactions and fluid retention, the recommended pre–medication regimen was oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. Anti-emetic regimens are recommended as per local clinical practice.

Treatment was administered until disease progression (symptomatic progressive disease, change of antineoplastic therapy), unacceptable toxicity, consent withdrawal or withdrawal from the study at the discretion of the Investigator or his/her designated associate(s), death, or non–compliance.

Objectives and endpoints

Table 26 : Objectives and endpoints

Primary endpoint	Definition
Overall survival (OS)	Time from the date of randomization until death from any cause. OS of patients not known to have died was censored at their last date of being known to be alive or at the database cut-off date, whichever came first.
Secondary endpoints	
Time to castration-resistant prostate cancer	Time from randomization to the first occurrence of one of the following events: • PSA progression, according to PCWG3 criteria with serum testosterone being at castrate level <0.50 ng/mL; defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir (lowest at or after baseline) was documented, both of which were confirmed by a second value obtained at least 3 weeks later, including all potential PSA values ≥2 ng/mL above nadir and ≥25% increase above nadir between the initial assessment date and the confirmation assessment date. This definition required serum testosterone at castrate levels <0.50 ng/mL and a first assessment date at least 12 weeks from randomization. The analysis was based on PSA and testosterone assessments from the central laboratory. However, due to the COVID-19 pandemic, some PSA assessments were performed at local laboratories. • Radiological progression by soft tissue and visceral lesions; defined according to RECIST v1.1, based on MRI/CT scans of the chest, abdomen, and pelvis performed by the investigator, as recommended by PCWG3 • Radiological progression by bone lesions; defined according to PCWG3 criteria based on whole body ^{99m}Tc methylene diphosphonate bone scans performed by the investigator.

Time to pain progression	Time from randomization to the first date a patient experienced pain progression. Pain progression was defined as: • For asymptomatic patients (worst pain subscale [WPS] = 0 at baseline, as assessed using the BPI-SF questionnaire [ePRO device]): - An increase of 2 or more points in the "worst pain in 24 hours" score (ie, 2 or more point increase in WPS score) from nadir (ie, zero) observed at 2 consecutive evaluations ≥4 weeks apart, or - Initiation of short- or long-acting opioid use for pain • For symptomatic patients (WPS >0 at baseline): - An increase of 2 or more points in the "worst pain in 24 hours" score (ie, 2 or more point increase in WPS score) from nadir observed at 2 consecutive evaluations ≥4 weeks apart and a WPS of ≥4, or - Initiation of short- or long-acting opioid use for pain
Symptomatic skeletal event-free survival (SSE-FS)	Time from randomization to the first occurrence of an SSE or death from any cause, whichever came first. An SSE was defined as the occurrence of one of the following: • Administration of EBRT to relieve skeletal symptoms, or • New symptomatic pathologic bone fracture, or • Spinal cord compression, or • Tumor-related orthopedic surgical intervention
Time to first symptomatic skeletal event (SSE)	Time from randomization to the first occurrence of an SSE. Death was not considered as an event.
Time to initiation of subsequent systemic antineoplastic therapy	Time from randomization to initiation of the first subsequent systemic antineoplastic therapy. Patients in the study may have received subsequent antineoplastic therapy for prostate cancer or for additional primary malignancies. Systemic antineoplastic therapy treatment was selected as described in the SAP.
Time to worsening of disease-related physical symptoms	Time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire (ePRO device). An increase in disease-related physical symptoms was defined as a 3-point decrease in the FPSI-DRS-P subscale from baseline (a lower score indicates a higher symptom burden), observed at 2 consecutive evaluations ≥4 weeks apart.
Time to initiation of opioid use for ≥7 consecutive days	Time from randomization to the date of first opioid use for ≥7 consecutive days. Opioid use related to prostate cancer pain was included in the analysis, while opioid use for non-malignant cause(s) was excluded.
<u>Exploratory endpoints</u>	
Time to PSA progression	Time from randomization to the date of first PSA progression (with testosterone at castrate level <0.5 ng/mL). The definition of PSA progression is the same as described above for the time to castration-resistant prostate cancer endpoint.
Rates of absolute and relative PSA response	Rate of response was determined by the number of patients with PSA response divided by the total number of patients randomized. • Absolute PSA response (evaluated at 6 and 12 months after randomization) was defined as a baseline PSA value above the detection limit and a post-baseline PSA level below 0.2 ng/mL, confirmed by a second subsequent PSA value below 0.2 ng/mL 3 or more weeks later, with all potential PSA values between the initial date and confirmation date below 0.2 ng/mL. • Relative 30% PSA response (evaluated at 3, 6, and 12 months after randomization) was defined as a baseline PSA value above the detection limit and a post-baseline ≥30% reduction in PSA level compared with the baseline value, confirmed by a second subsequent PSA value with a ≥30% reduction from baseline 3 or more weeks later, with all potential PSA values between the initial date and confirmation date showing a ≥30% reduction from baseline. Relative 50% and 90% PSA response were defined in the same way. In addition, descriptive statistics and frequency distribution (no decline, <30%, 30% to <50%, 50% to <90%, ≥90%) are provided for PSA maximum percent decline from baseline at any time on study.
ECOG Performance status	Summary group comparison of ECOG PS values by visit and changes from baseline

Quality of life (QoL):	ePRO data, as collected using the NCCN-FACT-FPSI-17 and BPI-SF questionnaires were analyzed to assess differences in QoL between the treatment arms.
NCCN-FACT-FPSI-17	Summary group comparison of total and subscore values by visit and changes from baseline
BPI-SF	Summary group comparison of total and subscore values by visit and changes from baseline; time-adjusted AUC

AUC=Area under the curve; BPI-SF=Brief pain inventory – short form; COVID-19=Coronavirus disease 2019; CT=Computed tomography; DRS-P=Disease-Related Symptoms Subscale – Physical; EBRT=External beam radiation therapy; ECOG PS=Eastern Cooperative Oncology Group performance status; eCRF=electronic case report form; ePRO=Electronic patient-reported outcome; MRI=Magnetic resonance imaging; NCCN-FACT-FPSI-17=National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy – Prostate Symptom Index 17-item questionnaire; OS =Overall survival; PCWG3=Prostate Cancer Working Group 3; PSA=Prostate-specific antigen; QoL=Quality of life; RECIST v1.1=Response evaluation criteria in solid tumor version 1.1; SAP=Statistical analysis plan; SSE=Symptomatic skeletal event; WPS=Worst pain subscale

Sample size

The sample size of the study was based on the primary endpoint of OS. The study was designed to have 90% power to detect a 25% decrease in risk of death with darolutamide compared with placebo with a one-sided test with a type I error of 0.025 (equivalent to a two-sided test with a type I error 0.05). The OS data were considered mature when approximately 509 deaths are observed.

With the additional assumptions that patients were enrolled at a rate of 50 patients per month, exponential distributions of the OS event times, median time of OS in the placebo group of 60 months, 5% dropout rate of patients, and a 6-months enrolment ramp-up period, it followed that approximately 1,300 patients were required to be randomized to observe 509 deaths after approximately 70 months.

Interim analysis

A futility interim analysis was planned. For the futility interim and final analyses together, a one-sided overall beta of 0.1 was used. Stopping boundaries were calculated with an O'Brien-Fleming beta-spending function using the actual number of events observed up to the cut-off date. The interim futility analysis was planned when approximately 153 deaths were observed (information fraction=0.3). The critical boundary for the futility analysis was calculated separately from the efficacy boundary, in order to not interfere with the type I error of the efficacy analysis.

Stopping boundaries for interim analysis

		Stopping Boundaries Hazard Ratio Scale (darolutamide+docetaxel arm vs. placebo+docetaxel arm) (% Improvement) / Z Score			
Analysis Time	# Events	Crossing Lower Bound (efficacy)	Crossing Upper Bound (futility - lack of efficacy)	Cumulative Alpha Spent	Cumulative Beta Spent
1st Interim[a]	153	-	1.166 (-14.2 %) / 0.952	-	0.003
Final	509	0.841 (19.0%) / 1.96	0.841 (19.0%) / 1.96	0.025	0.100

Software ADDPLAN neo V10.0.4 was used for this design

A second interim analysis was initially planned, which included a stopping boundary for efficacy calculated based on an alpha-spending function. It was removed with protocol amendment 7 (26 May 2020) due to the implications of the COVID–19 pandemic on the conduct of study procedures and data collection at the study sites.

The 1st interim analysis was completed and its stopping boundaries were calculated before the decision was made to remove the 2nd interim analysis.

Randomisation

Patients were randomly assigned on a 1:1 basis in a blinded fashion to treatment with darolutamide or matching placebo plus ADT and docetaxel. In addition, randomisation was stratified by:

- Extent of disease
    - Non–regional lymph nodes metastases only
    - Bone metastases with or without lymph node metastases
    - Visceral metastases with or without lymph node metastases or with or without bone metastases
- Alkaline Phosphatase
    - ALP<ULN
    - ALP≥ULN

Note: Blood samples to measure ALP levels for stratification were analysed in a central laboratory.

Blinding (masking)

Study ARESENS was a double-blind study. Both investigators and patients remained blinded to randomised treatment for the study duration.

Data monitoring committee (DMC)

A DMC was instituted to monitor ongoing safety of study patients with respect to a risk/benefit assessment during periodic data review meetings, review results from planned interim analyses and provide a formal recommendation for continuation/termination of the study and monitor study conduct to ensure the overall integrity of study was maintained. The DMC was to operate independently of the MAH and Investigators.

Statistical methods

Analysis populations

The Full Analysis Set was used for the analysis of all efficacy endpoints and all other endpoints. The Safety Analysis Set was used for the analyses of all safety endpoints. The pharmacokinetic data was analysed in the *pharmacokinetic analysis set (PKS).*

Full analysis set (FAS)

All patients who were randomized were included in the FAS, except for cases with critical GCP violations. Following the intent-to-treat principle, the patients in this set were grouped according to the planned treatment they were allocated to receive at randomization, irrespective of actual treatment.

Safety analysis set (SAF)

All randomized patients who received at least 1 dose of darolutamide or placebo were included in the SAF, except for cases with critical GCP violations. This safety population was used in the analyses of all

safety endpoints and was included in the analyses according to the treatment they actually received. Patients were included in the darolutamide + docetaxel + ADT arm if they had received any dose of darolutamide and were included in the placebo + docetaxel + ADT arm if they received only placebo.

Pharmacokinetic Analysis Set (PKS)

At least the first 20 randomized patients who received at least 1 cycle of docetaxel and for whom mandatory dense PK sampling was performed were included in the PKS. These patients received at least 3 days of uninterrupted study drug treatment, as well as one cycle of docetaxel and had at least one post-dose PK measurement, except for cases with critical GCP violations.

Multiplicity adjustment

If the primary endpoint OS was statistically significant at a 0.025 level (one-sided), the secondary endpoints were to be tested using a hierarchical test procedure in the order below at the same nominal significance level.

1) Time to castration-resistant prostate cancer

2) Time to pain progression

3) Symptomatic skeletal event free survival (SSE-FS)

4) Time to first symptomatic skeletal event (SSE)

5) Time to initiation of subsequent systemic antineoplastic therapy

6) Time to worsening of disease-related physical symptoms based on functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire (NCCN-FACT FPSI-17)

7) Time to initiation of opioid use for ≥ 7 consecutive days

If OS or a secondary endpoint was not statistically significant, the hierarchical procedure was stopped, and all subsequent analyses of the secondary endpoints were to be considered exploratory.

Interim analysis considerations

As described in the sample size section, a futility IA (not impacting the study type I error) was planned when approximately 153 deaths were observed (information fraction=0.3). This IA was completed.

A second interim analysis which included a stopping boundary for efficacy calculated based on an alpha-spending function was initially planned but was removed with protocol amendment 7 (26 May 2020) due to the implications of the COVID–19 pandemic on the conduct of study procedures and data collection at the study sites.

As a consequence, no alpha-spending function was used and the final analysis was performed using a one-sided test with a type I error of 0.025.

Primary endpoint

The primary efficacy endpoint was OS, defined as the time from the date of randomization until death from any cause. The censoring rules for OS are provided below.

Situation	End Date	Censored
Documented death during study before or at data cut-off date	Death date	No
No documented death with no contacts after randomization and before or at data cut-off date	Date of randomization (Day 1)	Yes
No documented death before or at data cut-off date	Last known alive date (LKAD) or at the data cut-off date, whichever comes earlier	Yes

The last known alive date (LKAD) was derived from the main data sources, i.e. visit dates, exposure information, laboratory measurements, tumor assessment dates, SSE dates, demographics, survival status date, vital signs and disposition events or follow up assessments were used to determine survival status.

The primary analysis of OS was a stratified log-rank test with the same IxRS stratification factors as were used for randomization. The HR (darolutamide or placebo) for OS and its 95% confidence interval (CI) were calculated using the Cox model, stratified by the same factors as were used for randomization. If the p-value from the one-sided log-rank test was less than 0.025 (corresponding to a two-sided log-rank test less than 0.05) with the HR (darolutamide + docetaxel + ADT arm vs. placebo + docetaxel + ADT arm) less than 1, the null hypothesis was rejected in favor of the alternative hypothesis.

Kaplan-Meier (KM) estimates for the median time of OS (including 95% CI) and 25% and 75% percentiles are presented for each treatment arm. KM estimates at time points such as 12 months, 24 months, etc., together with corresponding 95% CIs and the differences of these estimates between the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm were also presented.

Sensitivity analyses

OS was evaluated with the unstratified log-rank test and Cox model for the FAS population (OS sensitivity analysis 1 – unstratified analysis).

OS was to be also evaluated with the stratified log-rank test and Cox model for the FAS population using stratification factors collected from the eCRF, in case there were more than 5% of patients with different values in any stratification variable between IxRS and eCRF (OS sensitivity analysis 2 – eCRF-variables stratified analysis).

In addition, OS was evaluated with the stratified log-rank test and Cox model for the FAS population using extent of disease stratification factors collected from the central imaging review (OS sensitivity analysis 3 – central imaging review extent of disease as stratification factor).

<u>Secondary endpoints</u>

All secondary endpoints were time-to-event variables, which were analyzed using a stratified log-rank test with randomization stratification factors using IxRS data. Hazard ratios and 95% CIs were provided using the Cox model stratified by the same factors as were used for randomization.

Median time, 25th and 75th percentiles, and associated 95% CI of KM estimates are presented by treatment arm, as well as the number and percentage of censored observations. KM curves were generated for each treatment arm.

Subgroup analyses

Subgroup analyses were conducted for the primary efficacy endpoint OS, based on the FAS population. Descriptive statistics and HR estimates with 95% CI were to be provided for the subgroups listed below, provided that at least 10 total events are observed within the subgroup across the treatment arms. HRs were presented in forest plots. All subgroups analyses were performed using an unstratified Cox model.

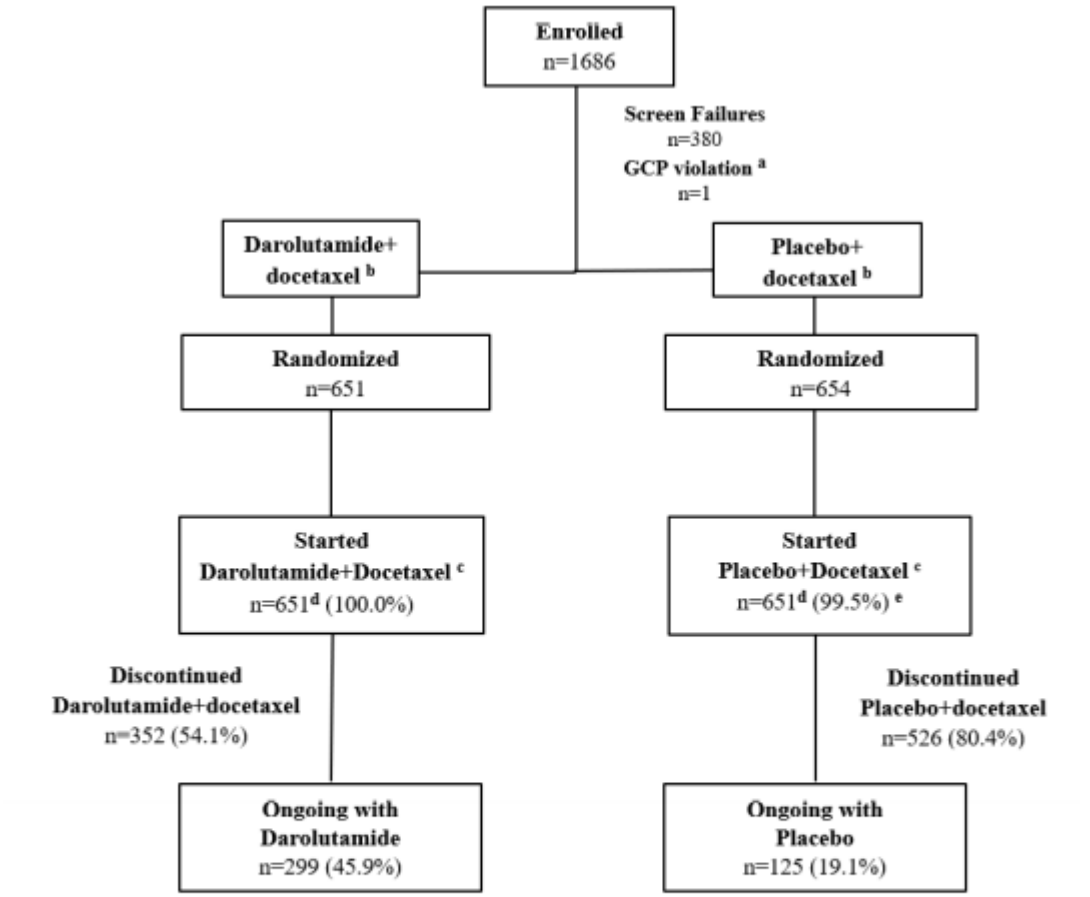
- Stratification Factor based on eCRF: Extent of disease (non-regional lymph nodes metastases only, bone metastases with or without lymph node metastases, or visceral metastases with or without lymph node metastases or with or without bone metastases)
- Stratification Factor based on eCRF: ALP at baseline (<ULN, ≥ULN)
- Age category (<65, 65-74, 75-84, ≥85 years)
- Race (White, Asian, Black or African American, Other)
- Geographical region (North America, Asia Pacific, Rest of the World)
- PSA values (<median of overall population, ≥median of overall population) at baseline
- ECOG PS at baseline (0, 1)
- Gleason score (<8, ≥8) at initial diagnosis
- Metastases at initial diagnosis (Yes: Stage IV-M1, No: Stage I, IIA, IIB, III, IV-M0)

Subgroup analysis

Subgroup analyses were conducted for the primary efficacy endpoint OS, based on the FAS population. Descriptive statistics and HR estimates with 95% CI were provided for the subgroups, provided that at least 10 total events were observed within the subgroup across both treatment arms. HRs were presented in forest plots. All subgroup analyses were performed using an unstratified Cox model. The number of patients, the number of events, and KM estimates for the median per arm for all planned subgroups were presented in the forest plot.

Results

Participant flow



Abbreviations: ADT=Androgen deprivation therapy; FAS=Full analysis set; GCP=Good clinical practice; n=number of patients
a: 1306 patients were randomized. One patient was excluded from analysis due to a GCP violation (Section 8.2.3).
b: ADT was administered throughout the entire study.
c: Docetaxel treatment was administered for only 6 cycles.
d: The number of patients who started treatment is presented based on the randomized treatment assignment. One patient was randomized to the placebo+docetaxel arm but received at least one dose of darolutamide. This patient was included in the darolutamide+docetaxel arm in the analysis of all safety variables (Section 8.3).
e: In total, 3 patients were randomized but were never administered study drug. All of these patients were in the placebo+docetaxel arm.

Figure 13 : ARASENS Study Flow Chart

Table 27 : Patient disposition at the time of database cut-off (25 OCT 2021) in Study 17777

Enrolled	**1686 [a]**	
Discontinued screening [b]	**380**	
	Darolutamide+ docetaxel arm N=651	**Placebo+ docetaxel arm N=654**
Randomized [c] (N=1305) (included in FAS)	**651 (100.0%)**	**654 (100.0%)**
Study drug never administered	0	3 (0.5%)
Started study treatment (N=1302) (included in SAF [d])	**651 (100.0%)**	**651 (99.5%)**
Discontinued study treatment	**352 (54.1%)**	**526 (80.4%)**
Primary reason:		
Progressive disease – clinical progression	127 (19.5%)	272 (41.6%)
Progressive disease – radiological progression	84 (12.9%)	132 (20.2%)
Adverse event not associated with clinical disease progression	48 (7.4%)	27 (4.1%)
Withdrawal by patient	25 (3.8%)	35 (5.4%)
Adverse event associated with clinical disease progression	24 (3.7%)	26 (4.0%)
Non-compliance with study drug	14 (2.2%)	12 (1.8%)
Additional primary malignancy	11 (1.7%)	6 (0.9%)
Death	8 (1.2%)	5 (0.8%)
COVID-19 related death [e]	0	0
Lost to follow-up	4 (0.6%)	1 (0.2%)
Other	3 (0.5%)	4 (0.6%)
COVID-19 pandemic-related other reason	0	1 (0.2%)
Physician decision	3 (0.5%)	6 (0.9%)
Protocol violation	1 (0.2%)	0
Ongoing with study treatment (as of the cut-off date)	**299 (45.9%)**	**125 (19.1%)**
Entered Active follow-up	**224 (34.4%)**	**381 (58.3%)**
Completed Active follow-up	**76 (11.7%)**	**167 (25.5%)**
Discontinued Active follow-up	**133 (20.4%)**	**185 (28.3%)**
Primary reason:		
Death	70 (10.8%)	87 (13.3%)
COVID-19 related death	1 (0.2%)	0
Other	25 (3.8%)	41 (6.3%)
COVID-19 pandemic-related other reason	2 (0.3%)	3 (0.5%)
Withdrawal by patient	25 (3.8%)	44 (6.7%)
Progressive disease – clinical progression	8 (1.2%)	8 (1.2%)
Progressive disease – radiological progression	3 (0.5%)	3 (0.5%)
Lost to follow-up	2 (0.3%)	2 (0.3%)
Ongoing with Active follow-up (as of the cut-off date)	**15 (2.3%)**	**29 (4.4%)**
Entered Survival follow-up	**224 (34.4%)**	**373 (57.0%)**
Discontinued Survival follow-up	**145 (22.3%)**	**207 (31.7%)**
Primary reason:		
Death	134 (20.6%)	196 (30.0%)
COVID-19 related death	1 (0.2%)	0
Withdrawal by patient	8 (1.2%)	8 (1.2%)
Lost to follow-up	3 (0.5%)	3 (0.5%)
Ongoing with Survival follow-up (as of the cut-off date)	**79 (12.1%)**	**166 (25.4%)**

COVID-19=Coronavirus disease 2019; FAS=Full analysis set; GCP=Good Clinical Practice; N=Total number of patients; SAF=Safety analysis set; TEAEs=Treatment-emergent adverse events a: A total of 122 patients were re-screened, of which only 95 were randomized to the study. Re-screened and then randomized patients were only counted once (last enrollment captured). b: Includes all patients who discontinued the screening period for any reason. c: A total of 1306 patients were randomized. One patient was excluded from all analyses due to a GCP violation (Module 5.3.5.1, Report PH-42024, Section 8.2.3)
d: The analysis sets in this table are presented based on the randomized treatment assignment. One patient was randomized to the placebo + docetaxel + ADT arm but received at least 1 dose of darolutamide. This patient was included in the darolutamide + docetaxel + ADT arm in the analysis of all safety variables.
e: Although there were 6 patients with fatal (Grade 5) TEAEs that were related to COVID-19 (Module 5.3.5.1, Report PH-42024, Section 10.3.7), none of these events were reported by the investigator as being the primary reason for discontinuation of the treatment period.

Recruitment

1306 patients were randomized (1 patient was excluded from all analyses due to a GCP violation) at 301 study centers in 23 countries/regions: Australia (5 centers), Belgium (7 centers), Brazil (9 centers), Bulgaria (7 centers), Canada (5 centers), China (36 centers), Czech Republic (7 centers), Finland (7 centers), France (17 centers), Germany (11 centers), Israel (8 centers), Italy (9 centers), Japan (45 centers), Mexico (6 centers), Netherlands (8 centers), Poland (6 centers), Russian Federation (10 centers), South Korea (12 centers), Spain (13 centers), Sweden (5 centers), Taiwan (5 centers), UK (8 centers), US (55 centers).

First patient enrolled: 30 November 2016

Last patient first visit: 05 June 2018

Data cut-off date: 25 October 2021

The analyses presented in this report are based on a data cut-off of 25 October 2021.

Conduct of the study

Protocol amendments:

The global versions of protocol or protocol amendments are presented below:

Substantial protocol changes:	**Protocol Amendment 1**, dated 20 SEP 2016, was valid only for centers located in China. The main modification was: • Addition of new China specific pharmacokinetic (PK) sub-study **Protocol Amendment 2**, dated 04 OCT 2016, was globally implemented. The main modifications were: • New drug-drug interaction data added • Clarification of PK analysis o Patients participating to the detailed PK analysis (dense PK sampling) had received at least one cycle of docetaxel o Clarified the timing of the sparse PK sampling o Additional analysis of docetaxel in all the randomized patients • Addition of non-protein-bound (free) testosterone analysis **Protocol Amendment 3**, dated 04 NOV 2016, was valid only for centers located in UK. The main modification was: • List of acceptable effective contraception methods to be used was added by request of the Medicines and Healthcare Products Regulatory Agency (MHRA) **Protocol Amendment 4**, dated 31 JAN 2017, was valid only for centers located in Japan. The main modification was: • Added reporting requirements for medical device failures for imported and non-approved third-party devices used in Bayer-sponsored clinical trials in Japan to the PMDA, IECs/IRBs and investigators **Protocol Amendment 5**, dated 12 FEB 2018, was globally implemented. The main modifications were: • New drug-drug interaction data added • Modification of the dosing language to align darolutamide dosing wording across the development program • Clarification of docetaxel dosage and administration in accordance with the label and clarified that the first cycle of docetaxel should be administered within 6 weeks after start of study drug instead of 6 weeks after randomization • Guidance on laboratory tests before each docetaxel cycle to be in line with docetaxel label requirements

- Clarification added for the evaluation of soft tissue and visceral lesions; these were to be performed using the same radiological methods and assessed by RECIST criteria
- ADT switch to LHRH agonist was added to the list of prohibited concomitant medications and treatments and a clarification was added to allow an ADT switch to an antagonist during study treatment
- Collection of whole blood sample for pharmacogenetics test allowed at other visits if missed at Visit 1
- Clarification added for:
    - Unblinding in non–emergency situations was not permitted
    - For PK sampling
    - For laboratory safety assessments

Protocol Amendment 6, dated 10 DEC 2019, was globally implemented. The main modifications were:

- Option to continue darolutamide treatment in a separate program was added for those patients who are ongoing on darolutamide treatment; patients assigned to placebo would discontinue treatment and complete the study
- Additional survival sweeps were added
- Detailed information on darolutamide drug-drug interactions was removed and information on the effect of darolutamide on the PK of docetaxel was updated
- Guidance and cautions for specific drug-drug interactions were removed based on new data on these interactions becoming available
- AE reporting was modified to clarify that disease progression should not be reported as an AE; only the associated signs and symptoms should be reported as AEs
- In a subset of patients, additional determination of total and free testosterone was added to be performed also at the EOT Visit

Protocol Amendment 7, dated 26 MAY 2020, was globally implemented. The main modifications were:

- Planned second interim analysis was removed due to the implications of the COVID–19 pandemic on the conduct of study procedures and data collection at the study sites. The risk for not achieving the needed quality of data for a formal analysis at that point in time

was considered to be too high

- Clarification added for biomarker analysis and reporting
- Added text regarding ranking of secondary endpoints
- Due to removal of interim analysis 2, the sentence regarding alpha–spending was removed and a statement about beta–spending was added for clarification

Protocol Amendment 8, dated 30 AUG 2021 was valid only for centers located in Japan. The main modifications were:

- To minimize the burden for subjects still enrolled after the study reached primary completion, the number of procedures will be reduced to a minimum, to guarantee patient treatment continuation and safety
- Japanese subjects will be provided the opportunity to continue treatment at the discretion of the investigator

Protocol deviation

The number of patients with important protocol deviations in each treatment arm and overall is summarised below.

Table 28 : Important protocol deviations (FAS)

	Protocol Deviations Overall		Protocol Deviations Related to COVID-19	
Protocol Deviation Category	**Darolutamide+ docetaxel arm N=651 n (%)**	**Placebo+ docetaxel arm N=654 n (%)**	**Darolutamide+ docetaxel arm N=651 n (%)**	**Placebo+ docetaxel arm N=654 n (%)**
Patients with any important deviation	477 (73.3%)	483 (73.9%)	103 (15.8%)	79 (12.1%)
Procedure deviations	370 (56.8%)	373 (57.0%)	103 (15.8%)	78 (11.9%)
Treatment deviations	237 (36.4%)	232 (35.5%)	0	1 (0.2%)
Excluded concomitant medication treatment	34 (5.2%)	53 (8.1%)	0	1 (0.2%)
Withdrawal criteria during treatment phase present but not withdrawn	47 (7.2%)	26 (4.0%)	0	1 (0.2%)
Inclusion/exclusion criteria not met but subject entered treatment	36 (5.5%)	46 (7.0%)	Not applicable	Not applicable
Time schedule deviations	3 (0.5%)	3 (0.5%)	Not applicable	Not applicable
Randomization errors	0	1 (0.2%)	Not applicable	Not applicable

Abbreviations: COVID-19=Coronavirus disease 2019; FAS=Full analysis set; N=Total number of patients (100%); n=Number of patients with event
The COVID-19 pandemic associated important deviations are a subset of the overall important deviations and thus are included in the overall number of patients with important protocol deviations.
Patients may have had more than one protocol deviation but are only counted once within each deviation category.

Changes to planned analyses

Several changes to planned analyses were implemented with protocol amendments or revisions to the statistical analysis plan (SAP).

A main update to the analysis plan was introduced with protocol amendment 7 (26 May 2020), which removed the second planned IA. The rationale provided for its removal was the implications of the COVID-19 pandemic for the conduct of study procedures and data collection at the study sites. In

addition, the secondary endpoints were ranked in a gatekeeping procedure as part of this same amendment.

The removal of the second IA was reflected in the SAP in version 3.0 (26 May 2020). The hierarchical gatekeeping procedure was implemented in version 4.0 (dated 22 September 2021) of the SAP.

With SAP version 4.1 (11 November 2021), a change in the analysis populations was introduced. Patients were to be excluded from all FAS, SAF, and PKS if they were related to or associated with any critical GCP violations that result in fraudulent patient data. After detection of issues with investigator fraud at one site, it was decided to exclude one affected patient from all analysis sets as these data could not be trusted.

Post-hoc analyses were described in a SAP supplement (version 1.0, 4 February 2022), which included a set of additional sensitivity analyses for the primary and secondary endpoints: OS by 6 cycles versus 5 and less cycles, OS by 6 and 5 cycles versus 4 and less cycles, OS including one patient with violation of GCP (based on all randomized patients), time to pain progression based on unconfirmed pain progression as event, time to pain progression based on 4 or more points increase in WPS score.

Baseline data

Table 29 : Summary of Key Demographic and Baseline Characteristics (FAS)

	Darolutamide+ docetaxel arm N=651 (100%)	Placebo+ docetaxel arm N=654 (100%)
Age (years)		
Mean (StD)	66.7 (7.9)	67.0 (7.8)
Median (Min, Max)	67.0 (41, 89)	67.0 (42, 86)
Age group (years), n (%)		
<65	243 (37.3%)	234 (35.8%)
65–74	303 (46.5%)	306 (46.8%)
75–84	102 (15.7%)	110 (16.8%)
≥85	3 (0.5%)	4 (0.6%)
Race, n (%)		
White	345 (53.0%)	333 (50.9%)
Black or African American	26 (4.0%)	28 (4.3%)
Asian	230 (35.3%)	245 (37.5%)
Other [a]	7 (1.1%)	2 (0.3%)
Not reported	43 (6.6%)	46 (7.0%)
Ethnicity, n (%)		
Hispanic or Latino	40 (6.1%)	49 (7.5%)
Not Hispanic or Latino	561 (86.2%)	557 (85.2%)
Not reported	50 (7.7%)	48 (7.3%)
Geographical region, n (%)		
North America	125 (19.2%)	119 (18.2%)
Asia Pacific	229 (35.2%)	244 (37.3%)
Rest of the world (ROW)	297 (45.6%)	291 (44.5%)
Body mass index group (kg/m^2), n (%)		
<20	45 (6.9%)	34 (5.2%)
20 – <25	254 (39.0%)	248 (37.9%)
25 – <30	240 (36.9%)	254 (38.8%)
≥30	108 (16.6%)	116 (17.7%)
Missing	4 (0.6%)	2 (0.3%)
Renal function - eGFR at baseline (mL/min) [b]		
Normal	375 (57.6%)	365 (55.8%)
Mild impairment	236 (36.3%)	235 (35.9%)
Moderate impairment	39 (6.0%)	53 (8.1%)
Severe impairment [c]	1 (0.2%)	0
Missing	0	1 (0.2%)
Hepatic function at baseline [d]		
Normal	597 (91.7%)	593 (90.7%)
Mild impairment	49 (7.5%)	52 (8.0%)
Moderate impairment	2 (0.3%)	0
Missing	3 (0.5%)	9 (1.4%)
Extent of metastatic disease at study entry (eCRF), n (%)		
M1a: Non-regional lymph nodes only	23 (3.5%)	16 (2.4%)
M1b: Bone with or without lymph nodes	517 (79.4%)	520 (79.5%)
M1c: Visceral with or without lymph nodes or bone	111 (17.1%)	118 (18.0%)
ALP at baseline (central laboratory[e]; eCRF) (U/L), n (%)		
ALP < ULN	290 (44.5%)	291 (44.5%)
ALP ≥ ULN	361 (55.5%)	363 (55.5%)
Stage of prostate cancer at initial diagnosis TNM classification)[f], n (%)		
Stage I	12 (1.8%)	10 (1.5%)
Stage IIA	18 (2.8%)	10 (1.5%)
Stage IIB	15 (2.3%)	10 (1.5%)
Stage III	36 (5.5%)	38 (5.8%)
Stage IV	563 (86.5%)	580 (88.7%)
Stage IV, M0	5 (0.8%)	14 (2.1%)
Stage IV, M1	558 (85.7%)	566 (86.5%)
Missing	7 (1.1%)	6 (0.9%)

	Darolutamide+ docetaxel arm N=651 (100%)	Placebo+ docetaxel arm N=654 (100%)
Gleason score at initial diagnosis of prostate cancer, n (%)		
<8	122 (18.7%)	118 (18.0%)
≥8	505 (77.6%)	516 (78.9%)
Missing	24 (3.7%)	20 (3.1%)
PSA at baseline (central laboratory) (ng/mL)		
n	651	653
Mean (StD)	248.47 (714.08)	204.71 (742.54)
Median (Min, Max)	30.30 (0.0, 9219.0)	24.20 (0.0, 11947.0)
Missing	0	1
ECOG Performance Status, n (%)		
0	466 (71.6%)	462 (70.6%)
1	185 (28.4%)	190 (29.1%)
Missing	0	2 (0.3%)
Testosterone at baseline (central laboratory) (ng/mL)		
<0.5	339 (52.1%)	353 (54.0%)
≥0.5	309 (47.5%)	296 (45.3%)
Missing	3 (0.5%)	5 (0.8%)

Abbreviations: AJCC = American Joint Committee on Cancer; ALP=Alkaline phosphatase; AST=Aspartate aminotransferase; eCRF=Electronic case report form; eGFR=Estimated glomerular filtration rate; ECOG=Eastern Cooperative Oncology Group; FAS=Full analysis set; Max=Maximum; Min=Minimum; N=Total number of patients (100%); n=Number of patients with event; PSA=Prostate-specific antigen; StD=Standard deviation; TNM=Tumor, Node, Metastasis; U/L=Unit per liter; ULN=Upper limit of normal

a: Race 'Other' includes "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", and "Multiple"

b: Renal function: normal: eGFR ≥90 mL/min; mild impairment: 60 ≤ eGFR <90 mL/min; moderate impairment: 30 ≤ eGFR <60 mL/min; severe impairment: 15 ≤ eGFR < 30 mL/min

c: 1 patient with severe renal impairment at baseline was eligible based on a serum creatinine level below ≤2.0 x ULN.

d: Hepatic function: normal: Total bilirubin and AST ≤ ULN; mild impairment: Total bilirubin and AST >ULN to 1.5x ULN or Total bilirubin ≤ ULN and AST >ULN; moderate impairment: Total bilirubin >1.5 to 3x ULN, any AST

e: For 2 patients (1 in the darolutamide+docetaxel arm and the other in the placebo+docetaxel arm), central laboratory ALP values were not available at baseline and the local laboratory ALP values were selected as baseline instead.

f: According to AJCC 7th edition, Stage IV could be M1 or M0 disease. For the purpose of this analysis, the Stage IV M0 group was defined as the time interval of >3 months between initial diagnosis and initial diagnosis of metastases.

Note: Data collection for race and ethnicity was not allowed in some countries (eg, France) due to local regulations.

Table 30 : Prior local treatment for prostate cancer at study entry in Study 17777 (FAS

Number of patients (%)	Darolutamide+ docetaxel arm N=651 n (%)	Placebo+ docetaxel arm N=654 n (%)
Status of primary tumor at study entry		
Primary tumor unresected	572 (87.9%)	582 (89.0%)
Prostatectomy	44 (6.8%)	42 (6.4%)
Surgery (not further specified)	31 (4.8%)	21 (3.2%)
TURP	8 (1.2%)	7 (1.1%)
Other	4 (0.6%)	3 (0.5%)
Radiation	28 (4.3%)	22 (3.4%)
No surgery (prostatectomy) and no radiation	546 (83.9%)	566 (86.5%)

FAS=Full analysis set; N=Total number of patients; n=Number of patients with event; TURP=Transurethral resection of the prostate

Table 31: Anti-hormonal therapy and orchiectomy at study entry in Study 17777 (FAS)

	Darolutamide+ docetaxel arm N=651 n (%)	Placebo+ docetaxel arm N=654 n (%)
Number (%) of patients with at least one ADT	**651 (100.0%)**	**652 (99.7%) [a]**
LHRH agonist/antagonist only	635 (97.5%)	635 (97.1%)
Orchiectomy only	11 (1.7%)	12 (1.8%)
LHRH agonist/antagonist and orchiectomy	5 (0.8%)	5 (0.8%)

ADT=Androgen deprivation therapy; ATC=Anatomical Therapeutic Chemical classification system; FAS=Full analysis set; LHRH=Luteinizing hormone-releasing hormone; N=Total number of patients (100%); n=Number of patients with event

Medications or procedures taken before the start of darolutamide/placebo are included in this table.

ADT was defined by ATC codes: L02BX, L02BB, H01CC, V98, G03HB, L02AE, H01CA.

a: Two patients in the placebo+docetaxel arm were not counted toward the patients with prior ADT treatment. One of these patients began ADT treatment on the same day of the first study drug administration and, therefore, the ADT treatment was captured as a concomitant medication. The other patient had prior ADT incorrectly reported in the database as of the cut-off date, which was corrected and is captured in the

Numbers analysed

The **FAS** included all patients randomized to receive darolutamide + docetaxel + ADT (651 patients) and placebo + docetaxel + ADT (654 patients).

Outcomes and estimation

Primary variables

At the time of the database cut-off date for the primary completion analysis (25 OCT 2021), a total of 533 OS events had occurred, with 229 deaths (35.2% of patients) in the darolutamide + docetaxel + ADT arm and 304 deaths (46.5% of patients) in the placebo + docetaxel + ADT arm.

The median follow-up time from randomisation to the last contact or death was 43.7 months in the darolutamide + docetaxel + ADT arm and 42.4 months in the placebo + docetaxel + ADT arm.

Table 32 : ARASENS: Overall survival in Study 17777 (FAS)

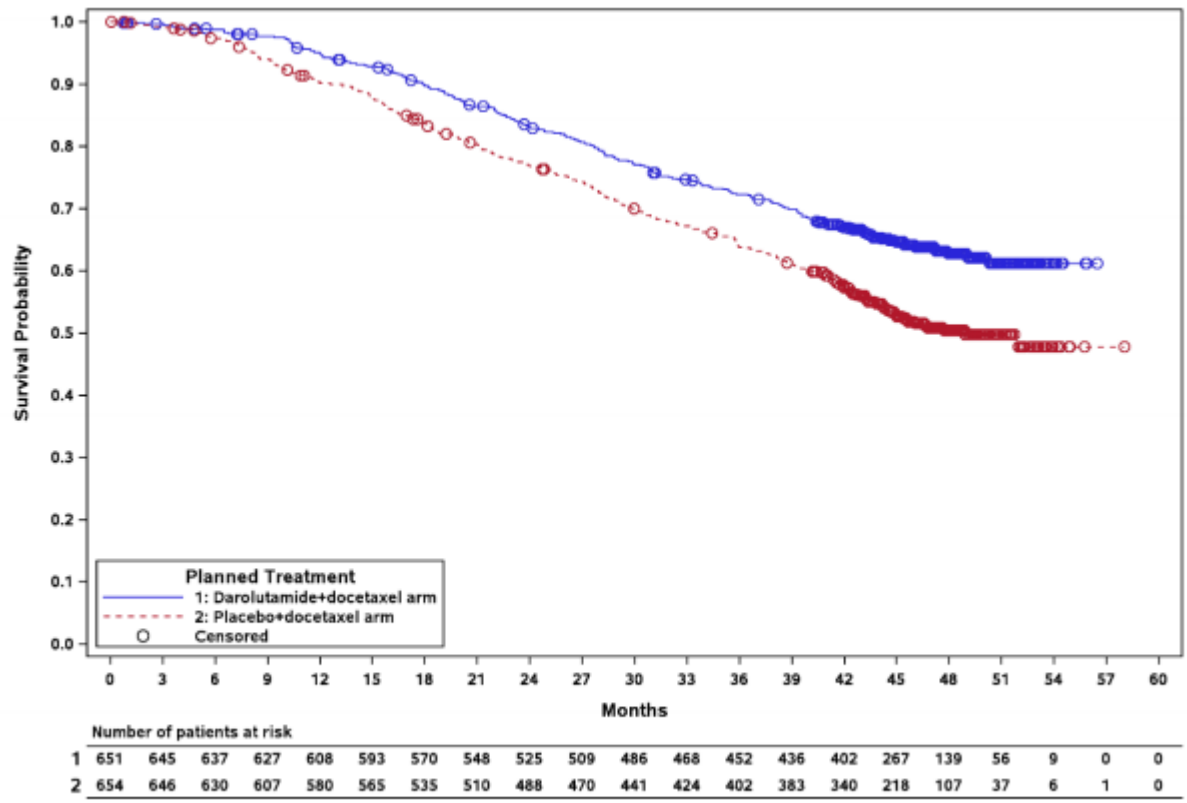
	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	229 (35.2%)	304 (46.5%)
Number (%) of patients censored	422 (64.8%)	350 (53.5%)
OS (months)		
Median [95% CI]	A [A; A]	48.9 [44.4; A]
Range (including censored values)	0.6–56.5**	0.1**–58.0**
12-month survival rate [95% CI]	0.949 [0.932; 0.966]	0.903 [0.880; 0.925]
24-month survival rate [95% CI]	0.831 [0.802; 0.860]	0.768 [0.735; 0.801]
36-month survival rate [95% CI]	0.723 [0.688; 0.758]	0.638 [0.601; 0.676]
48-month survival rate [95% CI]	0.627 [0.587; 0.667]	0.504 [0.463; 0.546]
Hazard ratio: (darolutamide vs. placebo) [95% CI] [a]	0.675 [0.568; 0.801]	
One-sided p-value from stratified log-rank test	<0.0001	

ALP=Alkaline phosphatase; CI=Confidence interval; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); OS=Overall survival; ULN=Upper limit of normal

** Censored observation; A=Value cannot be estimated due to censored data.

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox regression model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



FAS=Full analysis set

At-risk patient counts were calculated as at start of timepoint.

Figure 14 : Kaplan-Meier curves of overall survival in Study 17777 (FAS)

Key secondary endpoint

- **Time to castration-resistant prostate cancer**

Table 33 : Time to castration-resistant prostate cancer (FAS)

	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	225 (34.6%)	391 (59.8%)
PSA progression [a]	121/225 (53.8%)	289/391 (73.9%)
Radiological progression by bone lesions [a]	53/225 (23.6%)	53/391 (13.6%)
Radiological progression by soft tissue and visceral lesions [a]	51/225 (22.7%)	49/391 (12.5%)
Number (%) of patients censored	426 (65.4%)	263 (40.2%)
Time to CRPC (months)		
Median [95% CI]	A [A; A]	19.1 [16.5; 21.8]
Range (including censored values)	(0.03**–56.2**)	(0.03**–55.6**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [b]	0.357 [0.302; 0.421]	
One-sided p-value from stratified log-rank test	<0.0001	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; CRPC=Castration-resistant prostate cancer; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); PCWG3=Prostate Cancer Working Group 3; PSA=Prostate-specific antigen; RECIST v1.1=Response evaluation criteria in solid tumors version 1.1; ULN=Upper limit of normal

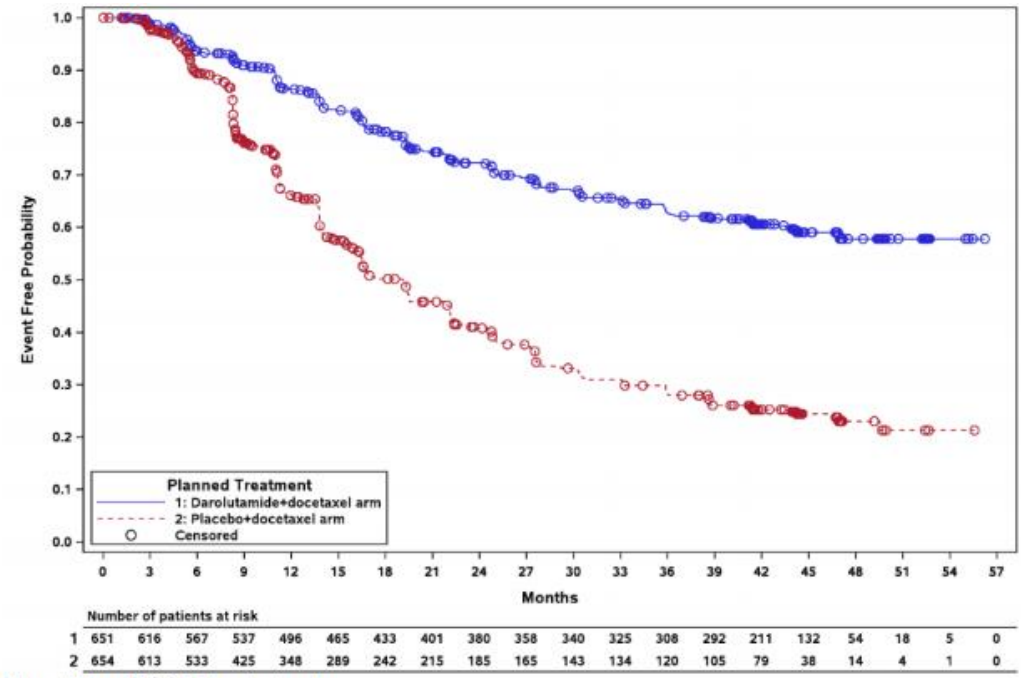
** Censored observation. A=Value cannot be estimated due to censored data.

a: Percentages by treatment arm are based on the number of patients with time to castration-resistant prostate cancer events. Patients with multiple events were only counted for the category in which the first event occurred. If multiple CRPC component events occurred on the same date for one patient, the patient was only counted in one category in the order of: radiological soft tissue/visceral lesion progression > radiological bone progression > PSA progression.

b: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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

Note: PSA progression and radiological progression by bone lesions were determined according to PCWG3 criteria. Radiological progression by soft tissue and visceral lesions are determined according to RECIST v1.1.



Abbreviations: FAS=Full analysis set

At-risk patient counts were calculated as at start of timepoint.

Figure 15 : Kaplan-Meier curves of time to castration-resistant prostate cancer (FAS)

- **Time to pain progression**

Table 34 : Time to pain progression (FAS)

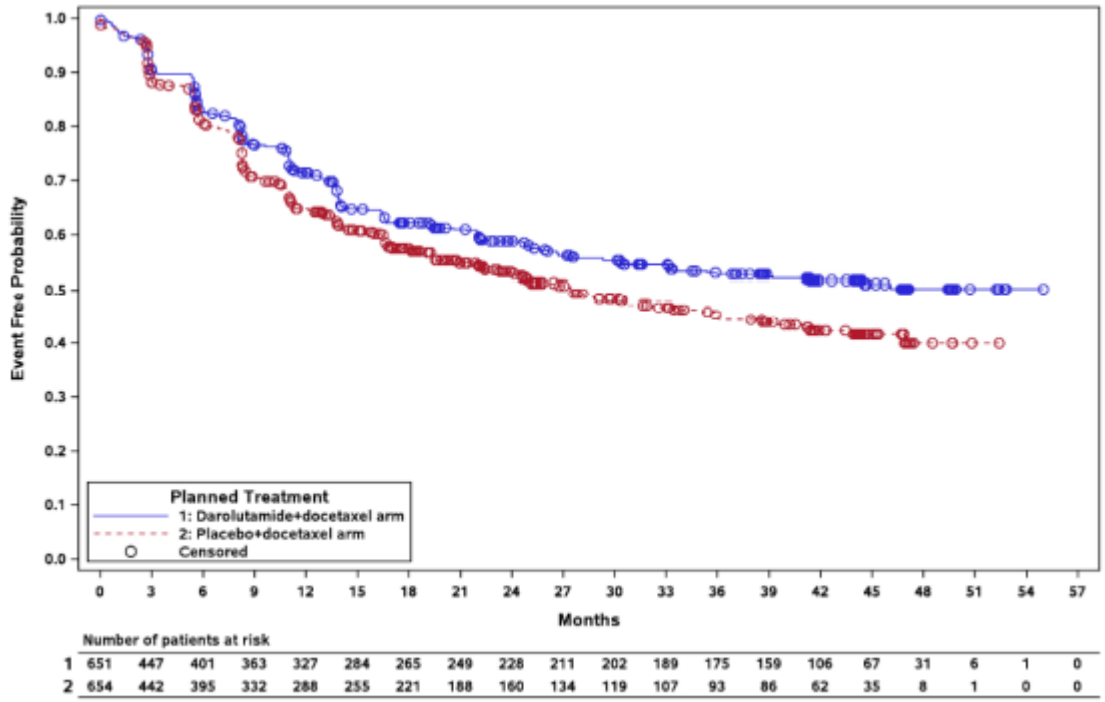
	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	222 (34.1%)	248 (37.9%)
Number (%) of patients censored	429 (65.9%)	406 (62.1%)
Time to pain progression (months)		
Median [95% CI]	A [30.5; A]	27.5 [22.0; 36.1]
Range (including censored values)	(0.03–55.0**)	(0.03–52.4**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [a]	0.792 [0.660; 0.950]	
One-sided p-value from stratified log-rank test	0.0058	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); ULN=Upper limit of normal

** Censored observation. A=Value cannot be estimated due to censored data.

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



Abbreviations: FAS=Full analysis set

At-risk patient counts were calculated as at start of timepoint.

Figure 16: Kaplan-Meier curves of time to pain progression (FAS)

- **SSE-FS**

Table 35 : Symptomatic skeletal event-free survival (FAS)

	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	257 (39.5%)	329 (50.3%)
Death [a]	162/257 (63.0%)	221/329 (67.2%)
EBRT to relieve skeletal symptoms [a]	60/257 (23.3%)	89/329 (27.1%)
New symptomatic pathologic bone fracture [a]	17/257 (6.6%)	8/329 (2.4%)
Spinal cord compression [a]	14/257 (5.4%)	9/329 (2.7%)
Tumor-related orthopedic surgical intervention [a]	4/257 (1.6%)	2/329 (0.6%)
Number (%) of patients censored	394 (60.5%)	325 (49.7%)
SSE-FS (months)		
Median [95% CI]	51.2 [47.2; A]	39.7 [36.0; 42.3]
Range (including censored values)	(0.03**–55.5**)	(0.03–55.6**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [b]	0.609 [0.516; 0.718]	
One-sided p-value from stratified log-rank test	<0.0001	

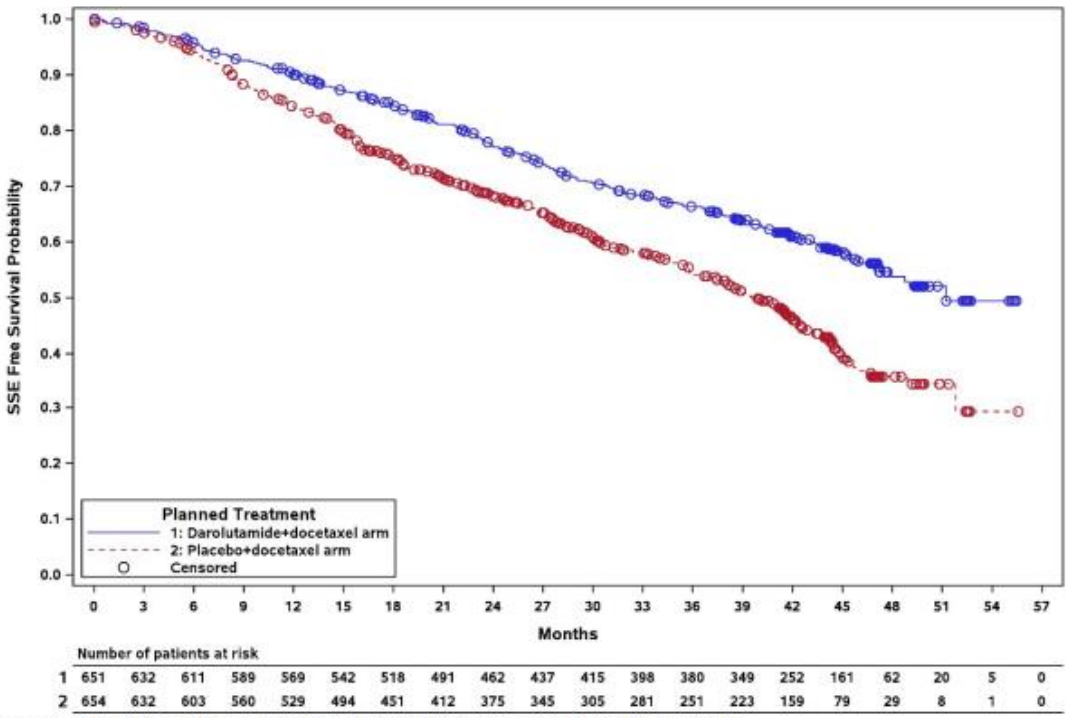
Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; EBRT=External beam radiation therapy; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); SSE-FS=Symptomatic skeletal event-free survival; ULN=Upper limit of normal

** Censored observation. A=Value cannot be estimated due to censored data.

a: Percentages are based on the total number of patients with an SSE-FS event in each treatment arm. Patients with multiple events were only counted for the category in which the first event occurred. If multiple SSEs (component events) occurred on the same date for one patient, the patient was only counted in one category in the order of: spinal cord compression > bone fracture > orthopedic surgery > EBRT.

b: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



Abbreviations: FAS=Full analysis set; SSE-FS=Symptomatic skeletal event-free survival
At-risk patient counts were calculated as at start of timepoint.

Figure 17 : Kaplan-Meier curves of SSE-FS (FAS)

- **Time to first SSE**

	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	95 (14.6%)	108 (16.5%)
External beam radiation therapy [a]	60/95 (63.2%)	89/108 (82.4%)
Symptomatic pathologic bone fracture [a]	17/95 (17.9%)	8/108 (7.4%)
Spinal cord compression [a]	14/95 (14.7%)	9/108 (8.3%)
Tumor-related orthopedic surgical intervention [a]	4/95 (4.2%)	2/108 (1.9%)
Number (%) of patients censored	556 (85.4%)	546 (83.5%)
Time to first SSE (months)		
Median [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03**–55.5**)	(0.03–55.6**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [b]	0.712 [0.539; 0.940]	
One-sided p-value from stratified log-rank test	0.0081	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; EBRT=External beam radiation therapy; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); SSE=Symptomatic skeletal event; ULN=Upper limit of normal

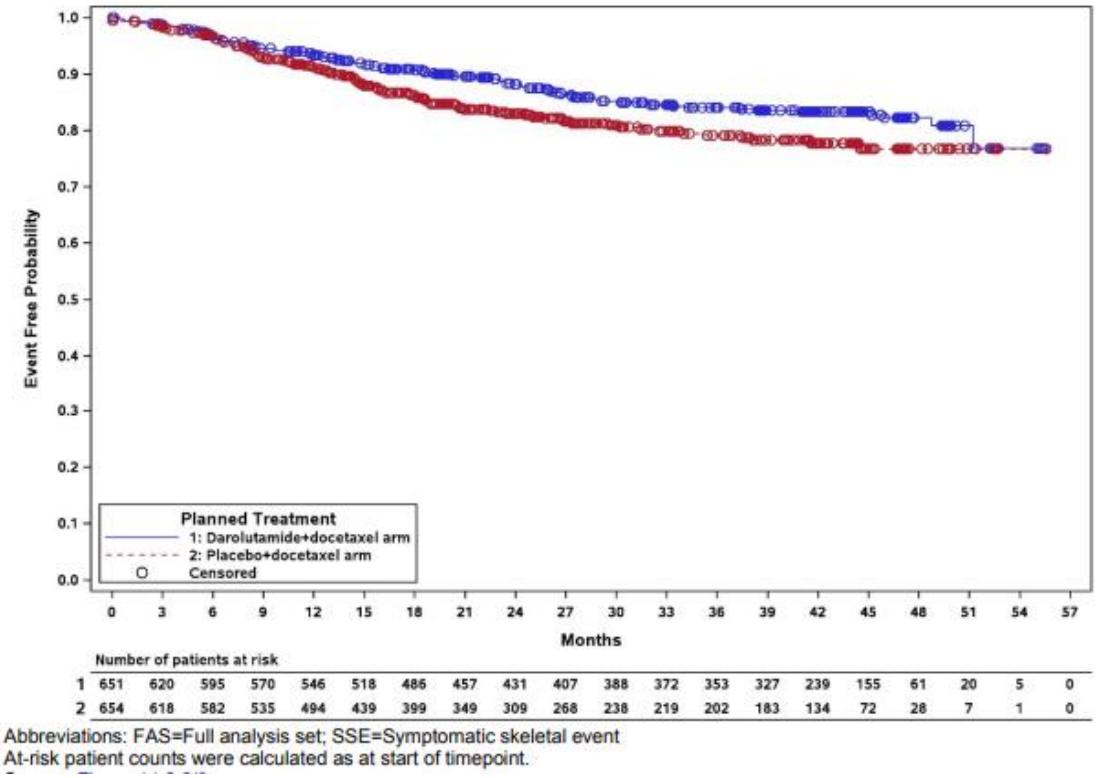
** Censored observation. A=Value cannot be estimated due to censored data.

a: Percentages are from the number of patients with an SSE in each treatment arm. Patients with multiple events were only counted for the category in which the first event occurred. If multiple SSEs (component events) occurred on the same date for one patient, the patient was only counted in one category in the order of: spinal cord compression > bone fracture > orthopedic surgery > EBRT.

b: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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

Figure 18 : Time to first symptomatic skeletal event (FAS)



Abbreviations: FAS=Full analysis set; SSE=Symptomatic skeletal event
At-risk patient counts were calculated as at start of timepoint.

Figure 19 : Kaplan-Meier curves of time to first SSE (FAS)

- **Time to initiation of subsequent systemic antineoplastic therapy**

Table 36 : Time to initiation of subsequent systemic antineoplastic therapy (FAS)

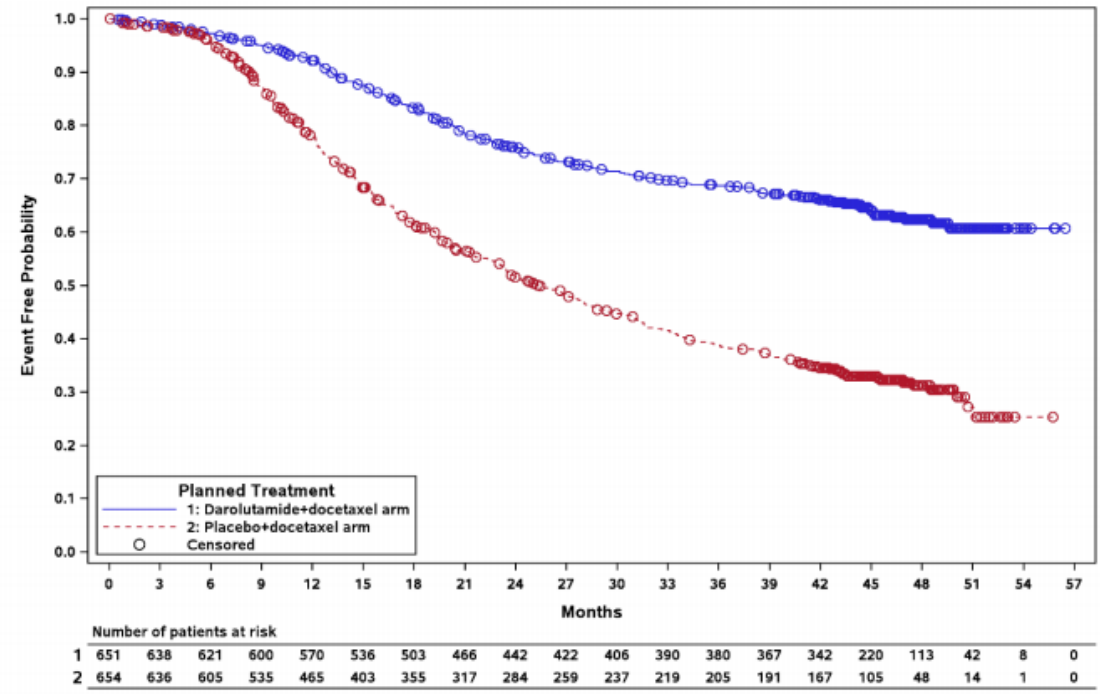
	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	219 (33.6%)	395 (60.4%)
Number (%) of patients censored	432 (66.4%)	259 (39.6%)
Time to initiation of subsequent systemic antineoplastic therapy (months)		
Median [95% CI]	A [A; A]	25.3 [23.1; 28.8]
Range (including censored values)	(0.2–56.5**)	(0.1**–55.7**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [a]	0.388 [0.328; 0.458]	
One-sided p-value from stratified log-rank test	<0.0001	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); ULN=Upper limit of normal

** Censored observation. A=Value cannot be estimated due to censored data.

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



FAS=Full analysis set

At-risk patient counts were calculated as at start of timepoint.

Figure 20 : Kaplan-Meier curves of time to initiation of subsequent systemic antineoplastic therapy in Study 17777 (FAS)

Table 37 : Summary of first subsequent systemic antineoplastic therapy after randomization by preferred drug name based on WHO-DD drug record number (full analysis set)

Preferred drug name(s) WHO-DD Version 2021SEP	Darolutamide+docetaxel arm N=651 (100%)	Placebo+docetaxel arm N=654 (100%)	Total N=1305 (100%)
Number (%) of patient with first systemic subsequent antineoplastic therapy	219 (33.6%)	395 (60.4%)	614 (47.0%)
ABIRATERONE, ABIRATERONE ACETATE	77 (11.8%)	178 (27.2%)	255 (19.5%)
ENZALUTAMIDE	25 (3.8%)	83 (12.7%)	108 (8.3%)
BICALUTAMIDE	27 (4.1%)	45 (6.9%)	72 (5.5%)
DOCETAXEL	25 (3.8%)	36 (5.5%)	61 (4.7%)
CABAZITAXEL, CABAZITAXEL ACETONE	24 (3.7%)	26 (4.0%)	50 (3.8%)
CARBOPLATIN	17 (2.6%)	5 (0.8%)	22 (1.7%)
ETOPOSIDE	12 (1.8%)	2 (0.3%)	14 (1.1%)
RADIUM RA 223 DICHLORIDE	8 (1.2%)	5 (0.8%)	13 (1.0%)
SIPULEUCEL-T	4 (0.6%)	7 (1.1%)	11 (0.8%)
CISPLATIN	6 (0.9%)	4 (0.6%)	10 (0.8%)
FLUTAMIDE	1 (0.2%)	3 (0.5%)	4 (0.3%)
PEMBROLIZUMAB	2 (0.3%)	2 (0.3%)	4 (0.3%)
ATEZOLIZUMAB	3 (0.5%)	0	3 (0.2%)
INVESTIGATIONAL DRUG	0	3 (0.5%)	3 (0.2%)
LUTETIUM (LU 177)	1 (0.2%)	2 (0.3%)	3 (0.2%)
PACLITAXEL, PACLITAXEL ALBUMIN	2 (0.3%)	1 (0.2%)	3 (0.2%)
ANTINEOPLASTIC AGENTS	1 (0.2%)	1 (0.2%)	2 (0.2%)
ESTRAMUSTINE, ESTRAMUSTINE PHOSPHATE	0	2 (0.3%)	2 (0.2%)
ETHINYLESTRADIOL	0	2 (0.3%)	2 (0.2%)
OLAPARIB	1 (0.2%)	1 (0.2%)	2 (0.2%)
APALUTAMIDE	1 (0.2%)	0	1 (<0.1%)
BLINDED THERAPY	0	1 (0.2%)	1 (<0.1%)
CATEQUENTINIB HYDROCHLORIDE	0	1 (0.2%)	1 (<0.1%)
DIETHYLSTILBESTROL	0	1 (0.2%)	1 (<0.1%)
GEMCITABINE	1 (0.2%)	0	1 (<0.1%)
GIMERACIL;OTERACIL POTASSIUM;TEGAFUR	1 (0.2%)	0	1 (<0.1%)
METHOTREXATE	1 (0.2%)	0	1 (<0.1%)
MITOXANTRONE	1 (0.2%)	0	1 (<0.1%)
NIVOLUMAB	0	1 (0.2%)	1 (<0.1%)
RITUXIMAB	1 (0.2%)	0	1 (<0.1%)
SORAFENIB TOSILATE	1 (0.2%)	0	1 (<0.1%)
TALAZOPARIB	0	1 (0.2%)	1 (<0.1%)

Note: Multiple subsequent systemic antineoplastic therapies for prostate cancer could occur on the same date, so a patient may be counted in more than one therapy.
The medications summarized in this table are all after randomization.
Patients with additional primary malignancies that received as subsequent systemic antineoplastic therapy for the additional primary malignancy are included in this table.
Preferred drug name is defined based on WHO-DD drug number, sequence #1 and sequence #2='001'
Different Preferred drug names listed under the same WHO-DD drug record number were combined.
Note: 13 patients started systemic antineoplastic medications during the treatment period are included.
Bayer: /var/swan/root/bhc/1841788/17777/stat/main01/prod/analysis/pgms/t_14_2_2_s21_adcm_adtte_isat.sas 07JAN2022 11:25
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- **Time to worsening of disease-related physical symptoms**

Table 38 : Time to worsening of disease-related physical symptoms (FAS)

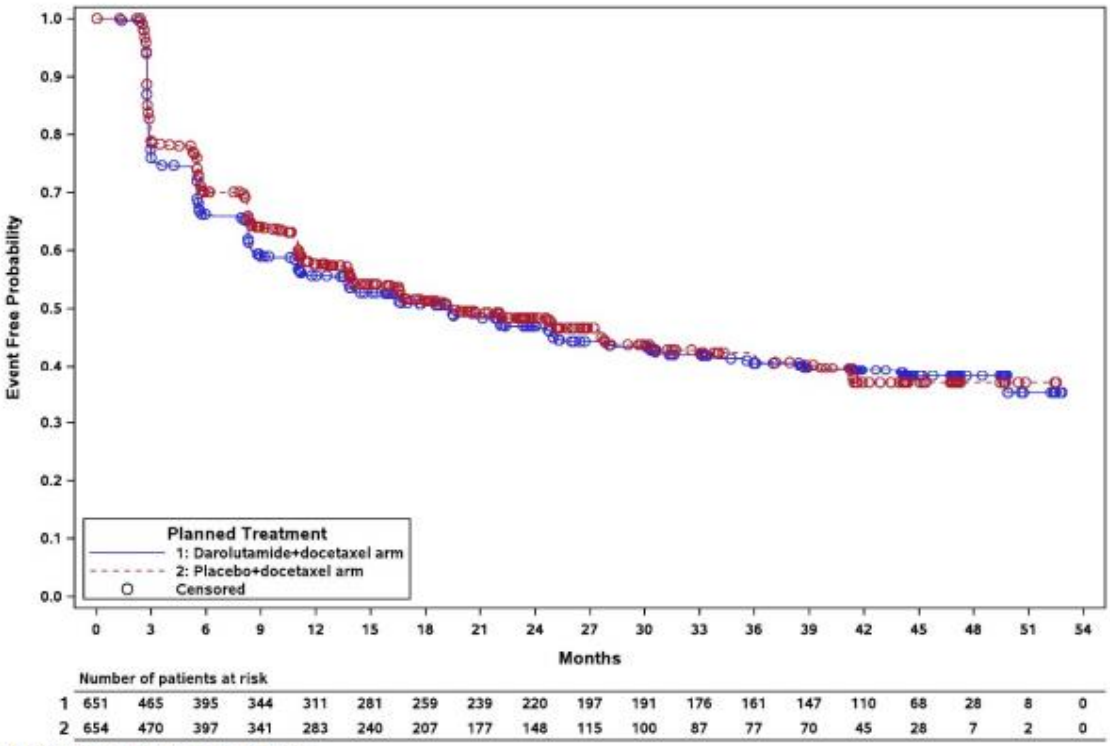
	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	351 (53.9%)	308 (47.1%)
Number (%) of patients censored	300 (46.1%)	346 (52.9%)
Time to worsening of disease-related physical symptoms (months)		
Median [95% CI]	19.3 [13.8; 24.8]	19.4 [15.4; 27.6]
Range (including censored values)	(0.03**–52.8**)	(0.03**–52.5**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [a]	1.043 [0.894; 1.217]	
One-sided p-value from stratified log-rank test	0.7073	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); ULN=Upper limit of normal

** Censored observation. A=Value cannot be estimated due to censored data.

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



Abbreviations: FAS=Full analysis set
At-risk patient counts were calculated as at start of timepoint.

Figure 21 : Kaplan-Meier curves of time to worsening of disease-related physical symptoms (FAS)

- **Time to initiation of opioid use for ≥7 consecutive days**

Table 39 : Time to initiation of opioid use for ≥7 consecutive days (FAS)

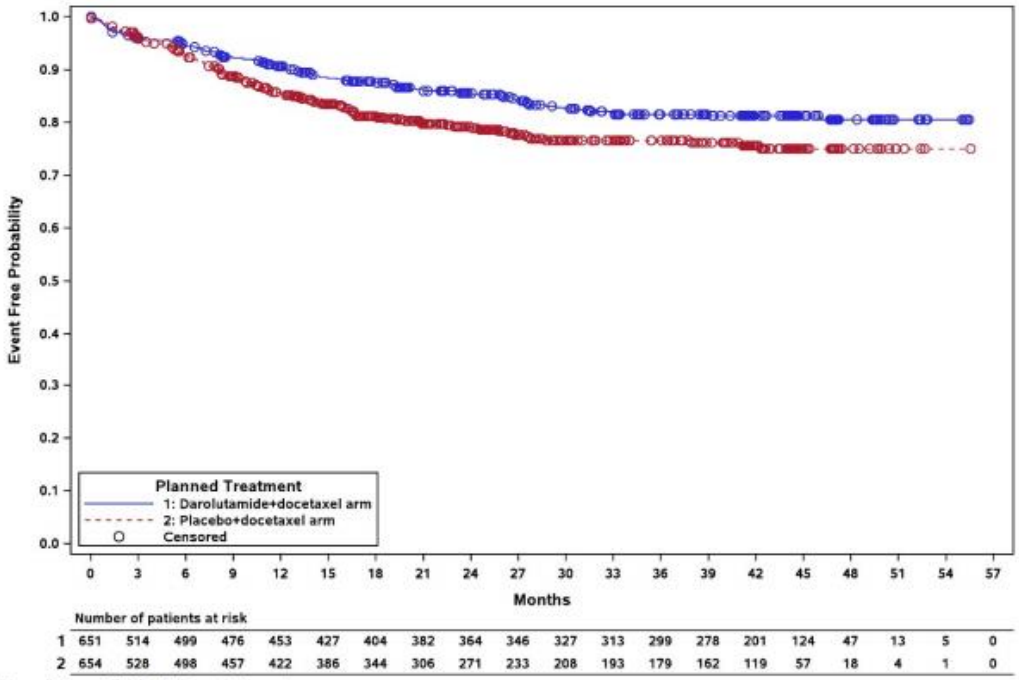
	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	92 (14.1%)	117 (17.9%)
Number (%) of patients censored	559 (85.9%)	537 (82.1%)
Time (months) to initiation of opioid use for ≥7 consecutive days		
Median [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03**–55.5**)	(0.03–55.6**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [a]	0.688 [0.523; 0.906]	
One-sided p-value from stratified log-rank test	0.0037	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); ULN=Upper limit of normal

** Censored observation. A=Value cannot be estimated due to censored data.

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



Abbreviations: FAS=Full analysis set
At-risk patient counts were calculated as at start of timepoint.

Figure 22 : Kaplan-Meier curves of time to initiation of opioid use for ≥7 consecutive days (FAS)

Exploratory secondary endpoints

- **Time to PSA Progression**

Table 40 : Time to PSA progression according to PCWG3 (FAS)

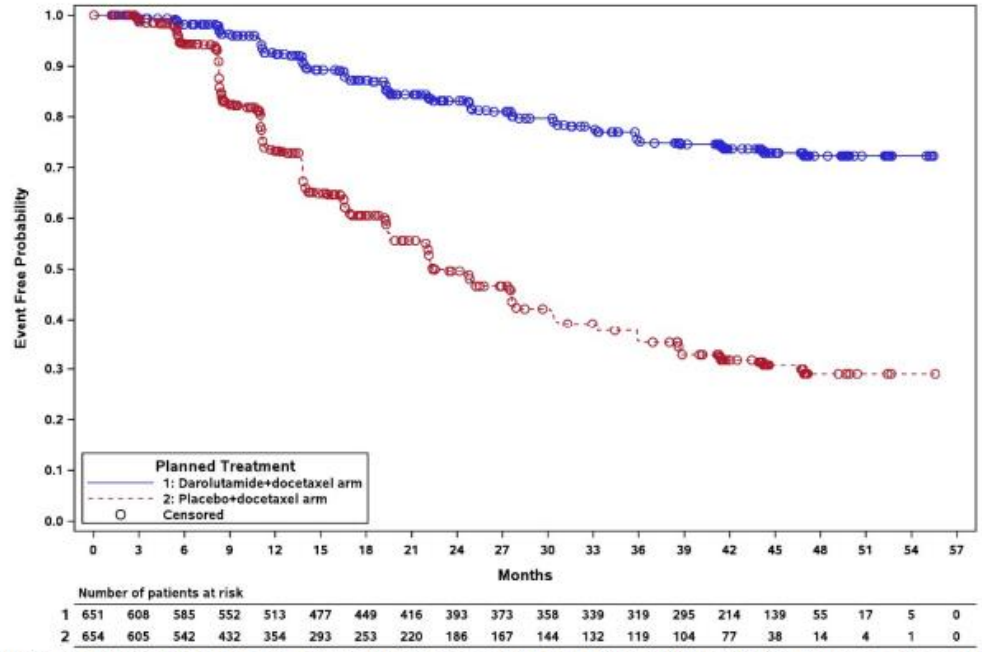
	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
Number (%) of patients with event	136 (20.9%)	310 (47.4%)
Number (%) of patients censored	515 (79.1%)	344 (52.6%)
Time to PSA progression (months)		
Median [95% CI]	A [A; A]	22.4 [22.1; 27.6]
Range (including censored values)	(0.03**–55.5**)	(0.03**–55.6**)
Hazard ratio: (darolutamide vs. placebo) [95% CI] [a]	0.255 [0.208; 0.313]	
One-sided p-value from stratified log-rank test	<0.0001	

Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; FAS=Full analysis set; M1a/M1b/M1c=classification of metastatic disease; N=Total number of patients (100%); PCWG3=Prostate Cancer Clinical Trials Working Group 3; PSA=Prostate-specific antigen; ULN=Upper limit of normal

** Censored observation. A=Value cannot be estimated due to censored data

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ≥ULN).

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



Abbreviations: FAS=Full analysis set; PCWG3=Prostate Cancer Clinical Trials Working Group 3; PSA=Prostate-specific antigen
At-risk patient counts were calculated as at start of timepoint.

Figure 23 : Kaplan-Meier curves of time to PSA progression according to PCWG3

- **PSA Response**

Table 41: Maximum percent decline in PSA from baseline at any time on study (FAS)

Maximum decline in PSA from baseline	Darolutamide+ docetaxel arm N=651	Placebo+ docetaxel arm N=654
No decline [a]	8 (1.2%)	22 (3.4%)
<30%	1 (0.2%)	11 (1.7%)
≥30% and <50%	5 (0.8%)	19 (2.9%)
≥50% and <90%	44 (6.8%)	135 (20.6%)
≥90%	577 (88.6%)	449 (68.7%)
Missing [b]	16 (2.5%)	17 (2.6%)

Abbreviations: FAS=Full analysis set; N=Total number of patients (100%); PSA=Prostate-specific antigen
Note: Only patients with PSA not missing at baseline are included in this table.
a: A negative percent indicates a decline in PSA, whereas a positive percent indicates that the patients never had a decline in PSA.
b: No post baseline value.

Table 42 : PSA response rates (FAS)

	Darolutamide+ docetaxel arm N=651		Placebo+ docetaxel arm N=654	
Absolute PSA response rate *(PSA level <0.2 ng/mL)* [a]	**n (%)**	**[95% CI]**	**n (%)**	**[95% CI]**
At 6 months from randomization	317 (48.7%)	[44.8%; 52.6%]	156 (23.9%)	[20.6%; 27.3%]
At 12 months from randomization	392 (60.2%)	[56.3%; 64.0%]	171 (26.1%)	[22.8%; 29.7%]
Relative PSA response rate *(≥90% reduction in PSA from baseline)* [b]				
At 6 months from randomization	534 (82.0%)	[78.9%; 84.9%]	356 (54.4%)	[50.5%; 58.3%]
At 12 months from randomization	549 (84.3%)	[81.3%; 87.0%]	376 (57.5%)	[53.6%; 61.3%]

Abbreviations: CI=Confidence interval; FAS=Full analysis set; N=Total number of patients (100%); n=Number of patients; PSA=Prostate-specific antigen

- **ECOG PS**

Table 43: ECOG Performance status - shift tables of change from baseline to worst score of post-baseline (full analysis set)

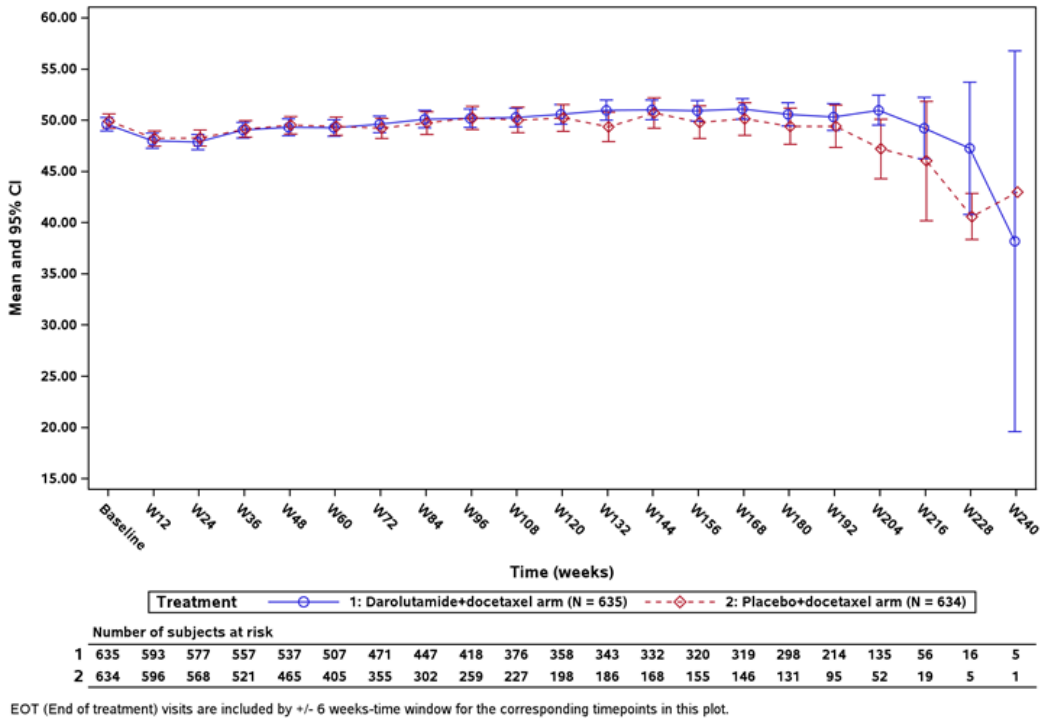
Treatment	Baseline	Worst post-baseline ECOG-PS score during treatment						
		0	1	2	3	4	Missing	Total
Darolutamide+docetaxel arm (N=651)	0	230 (35.3%)	198 (30.4%)	21 (3.2%)	7 (1.1%)	0	10 (1.5%)	466 (71.6%)
	1	15 (2.3%)	134 (20.6%)	28 (4.3%)	7 (1.1%)	0	1 (0.2%)	185 (28.4%)
	Missing	0	0	0	0	0	0	0
	Total	245 (37.6%)	332 (51.0%)	49 (7.5%)	14 (2.2%)	0	11 (1.7%)	651 (100.0%)
Placebo+docetaxel arm (N=654)	0	241 (36.9%)	181 (27.7%)	25 (3.8%)	8 (1.2%)	2 (0.3%)	5 (0.8%)	462 (70.6%)
	1	15 (2.3%)	137 (20.9%)	24 (3.7%)	6 (0.9%)	0	8 (1.2%)	190 (29.1%)
	Missing	0	0	2 (0.3%)	0	0	0	2 (0.3%)
	Total	256 (39.1%)	318 (48.6%)	51 (7.8%)	14 (2.1%)	2 (0.3%)	13 (2.0%)	654 (100.0%)

Note: Baseline ECOG value is the last non-missing observation on or before the randomization date.

- **Quality of life**

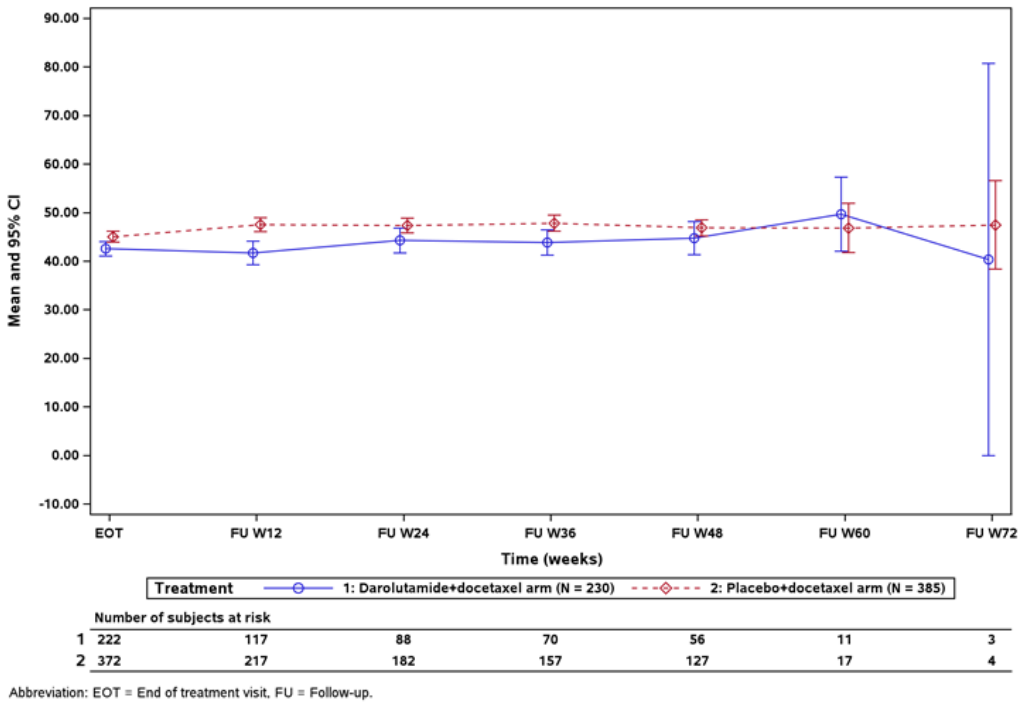
QoL of patients during the study was evaluated with the NCCN-FACT-FPSI-17 and the BPI-SF questionnaires. The NCCN-FACT-FPSI-17 questionnaire was used to assess symptoms of prostate cancer, symptoms of treatment of prostate cancer, and HRQoL in prostate cancer patients. The BPI-SF questionnaire was used to assess clinical pain. Results of question 3 in the BPI-SF, "worst pain in 24 hours," were used for the analysis of time to pain progression, a secondary efficacy endpoint.

NCCN-FACT FPSI-17 questionnaire - total score and subscale scores



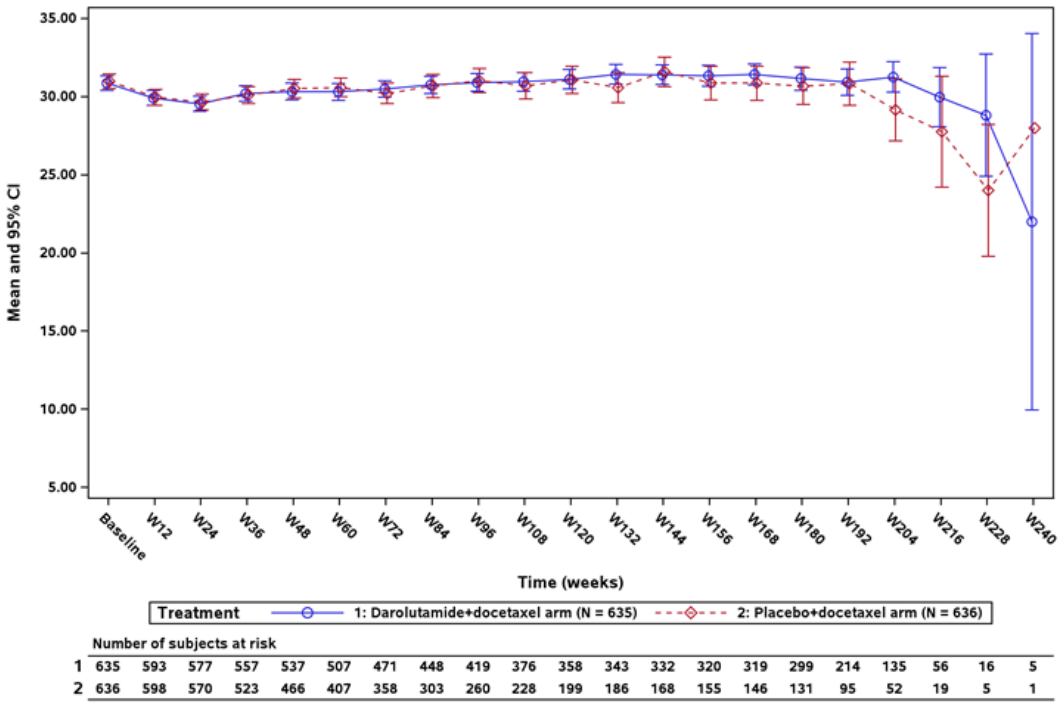
EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

Figure 24 a: NCCN-FACT FPSI 17 questionnaire during treatment period - means with 95% CI: FPSI-17 Total Score (FAS)



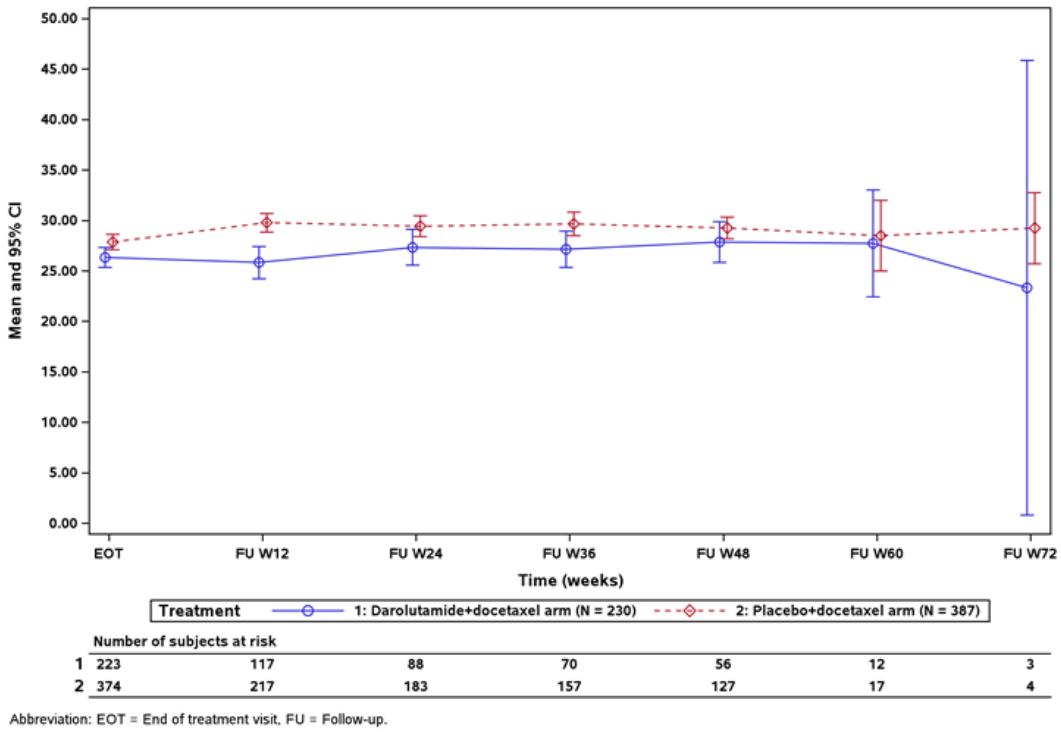
Abbreviation: EOT = End of treatment visit, FU = Follow-up.

Figure 25 b: NCCN-FACT FPSI 17 questionnaire during follow-up period - means with 95% CI: FPSI-17 Total Score (FAS)



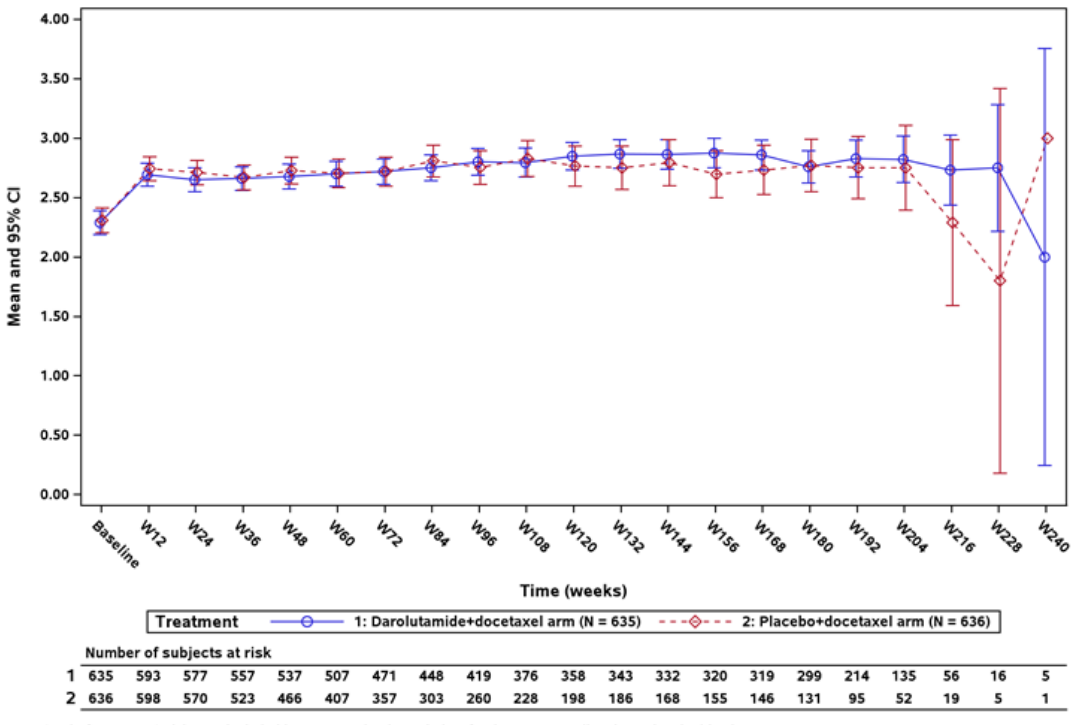
EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

Figure 26 a : NCCN-FACT FPSI 17 questionnaire during treatment period - means with 95% CI: Disease-related symptoms subscale - physical (DRS-P) Score (full analysis set)



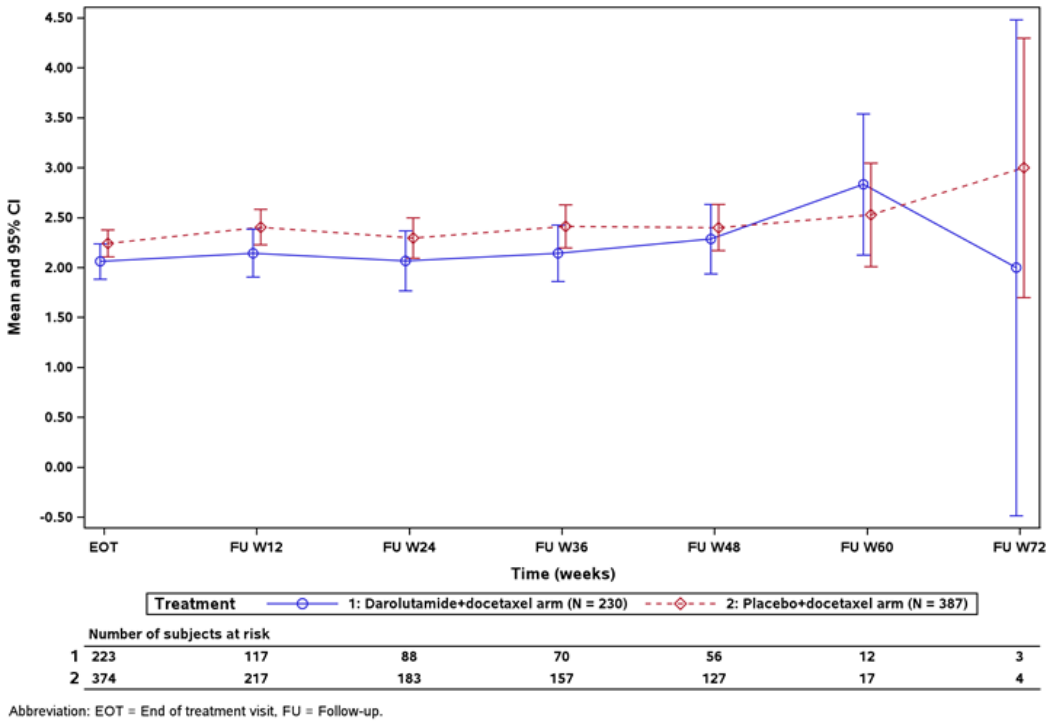
Abbreviation: EOT = End of treatment visit, FU = Follow-up.

Figure 27 b : NCCN-FACT FPSI 17 questionnaire during follow-up period - means with 95% CI: Disease-related symptoms subscale - physical (DRS-P) Score (full analysis set)



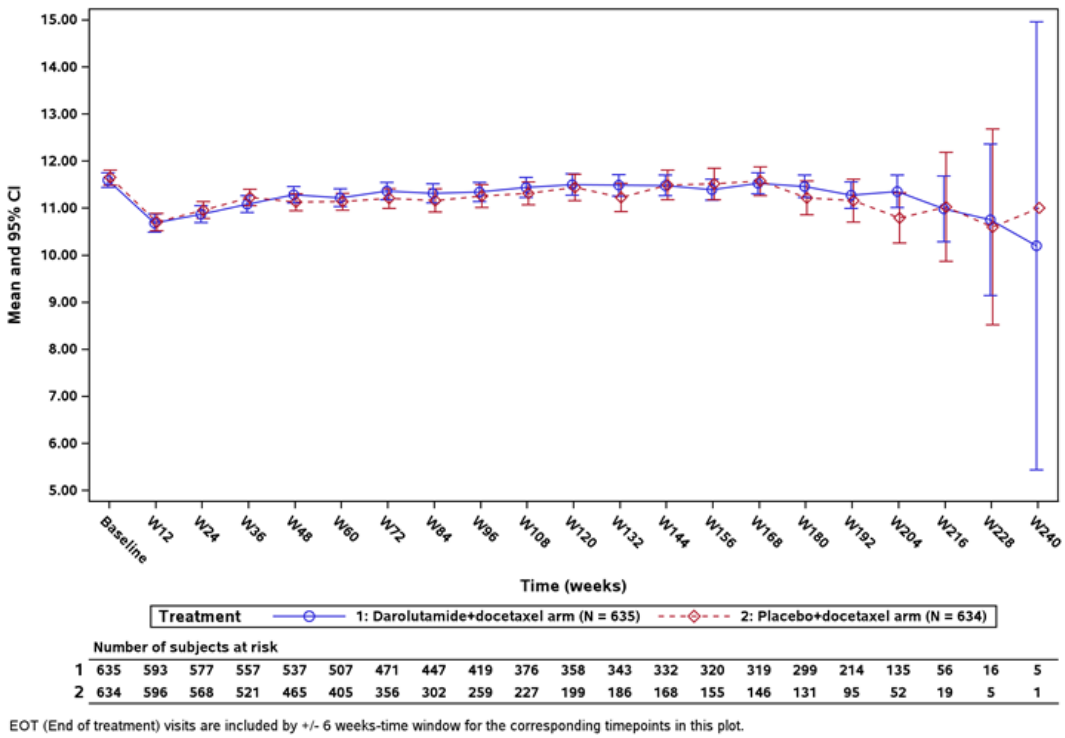
EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

Figure 28 a: NCCN-FACT FPSI 17 questionnaire during treatment period - means with 95% CI: Disease-related symptoms subscale - emotional (DRS-E) Score (full analysis set)



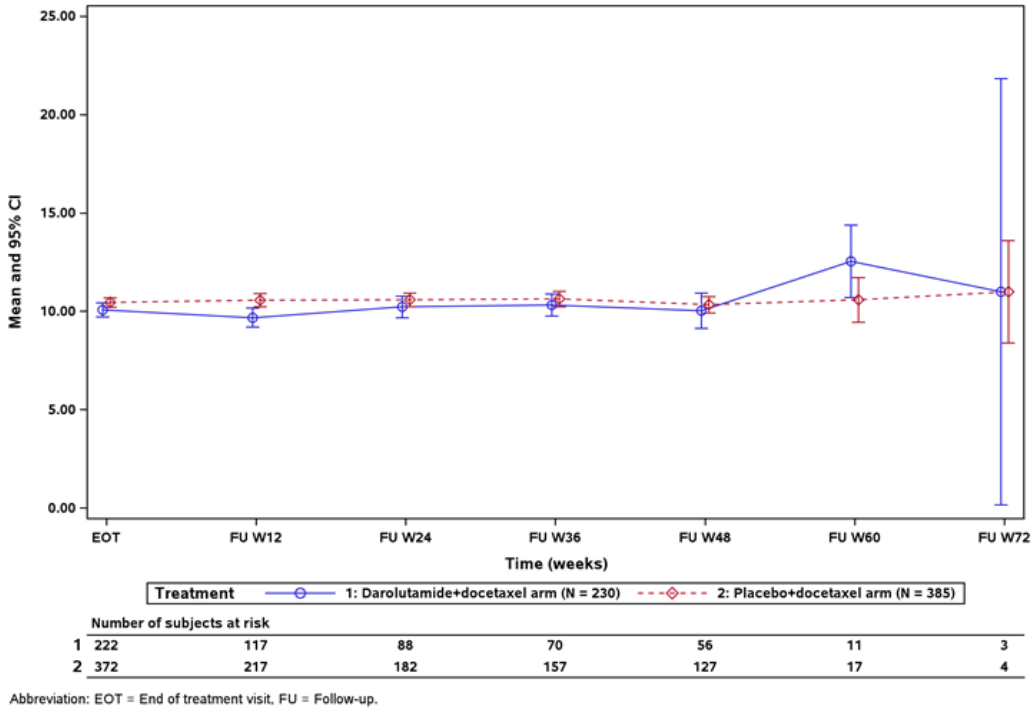
Abbreviation: EOT = End of treatment visit, FU = Follow-up.

Figure 29 b: NCCN-FACT FPSI 17 questionnaire during follow-up period - means with 95% CI: Disease-related symptoms subscale - emotional (DRS-E) Score (full analysis set)



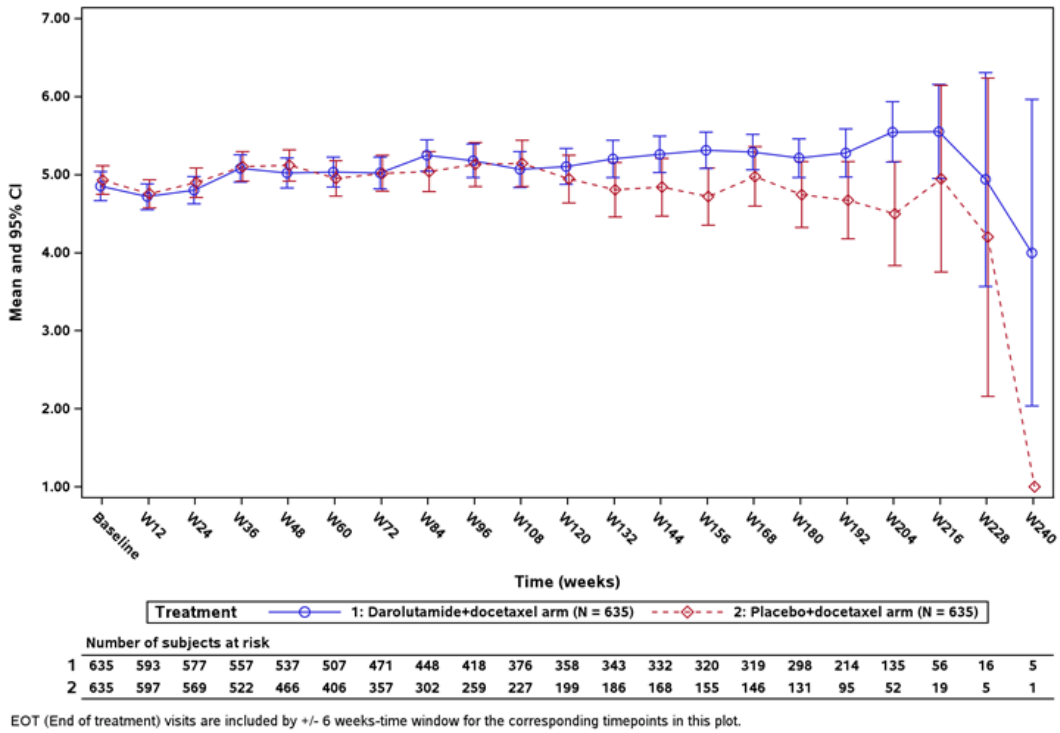
EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

Figure 30 a: NCCN-FACT FPSI 17 questionnaire during treatment period - means with 95% CI: Treatment side effects subscale (TSE) Score (full analysis set)



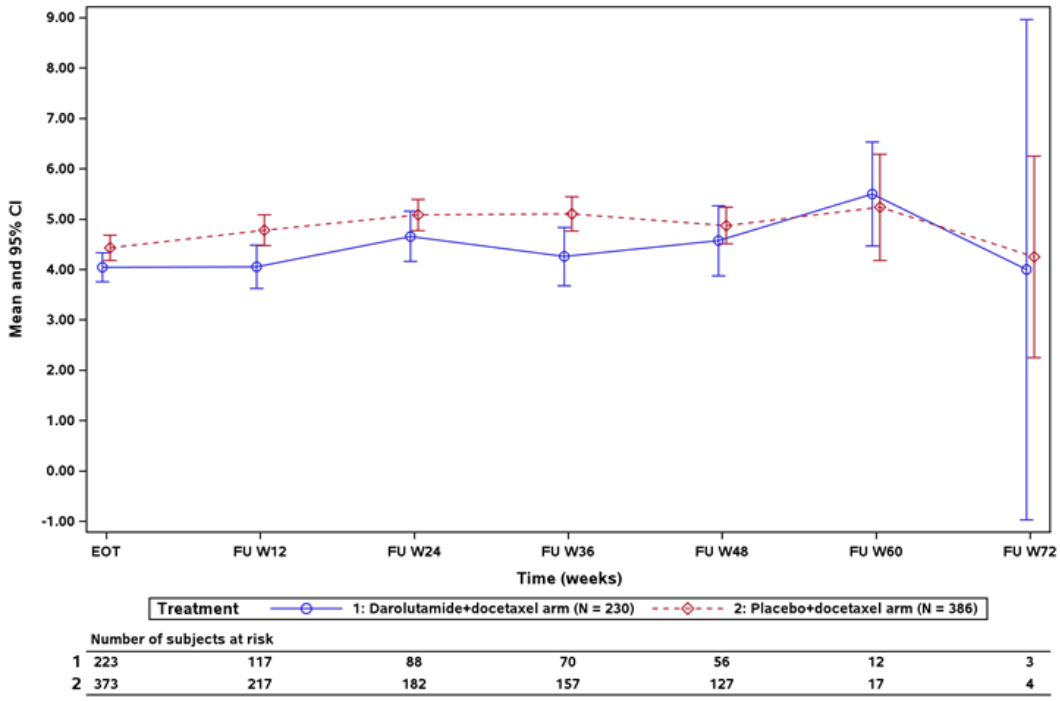
Abbreviation: EOT = End of treatment visit, FU = Follow-up.

Figure 31 b: NCCN-FACT FPSI 17 questionnaire during follow-up period - means with 95% CI: Treatment side effects subscale (TSE) Score (full analysis set)



EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

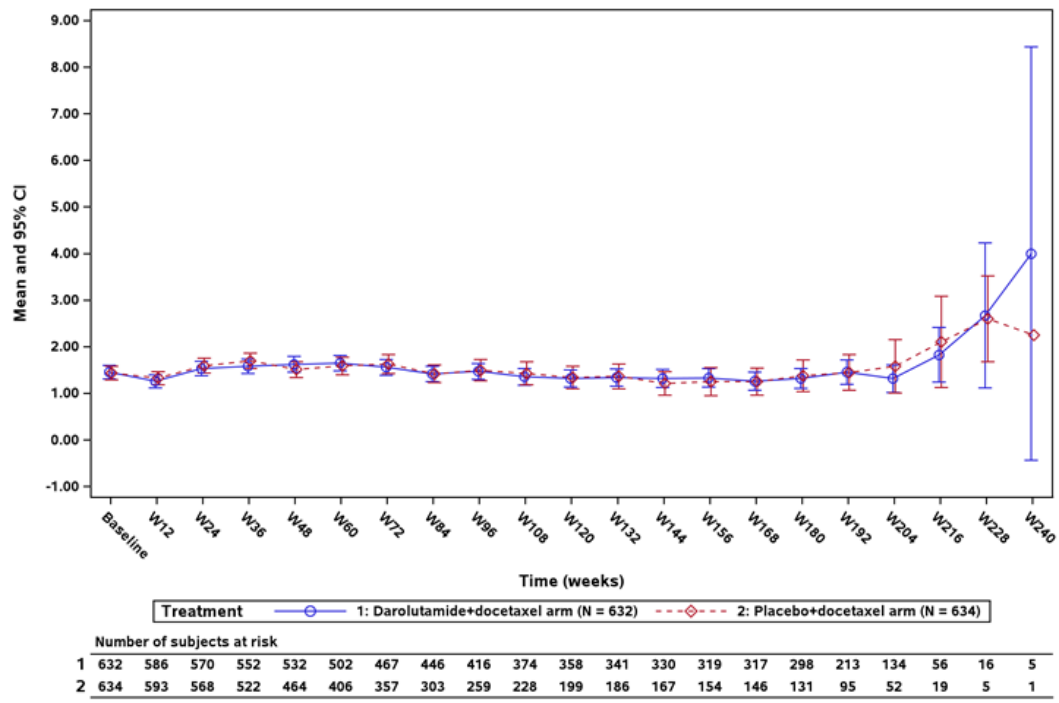
Figure 32a: NCCN-FACT FPSI 17 questionnaire during treatment period - means with 95% CI: Function and well-being subscale (FWB) Score (full analysis set)



Abbreviation: EOT = End of treatment visit, FU = Follow-up.

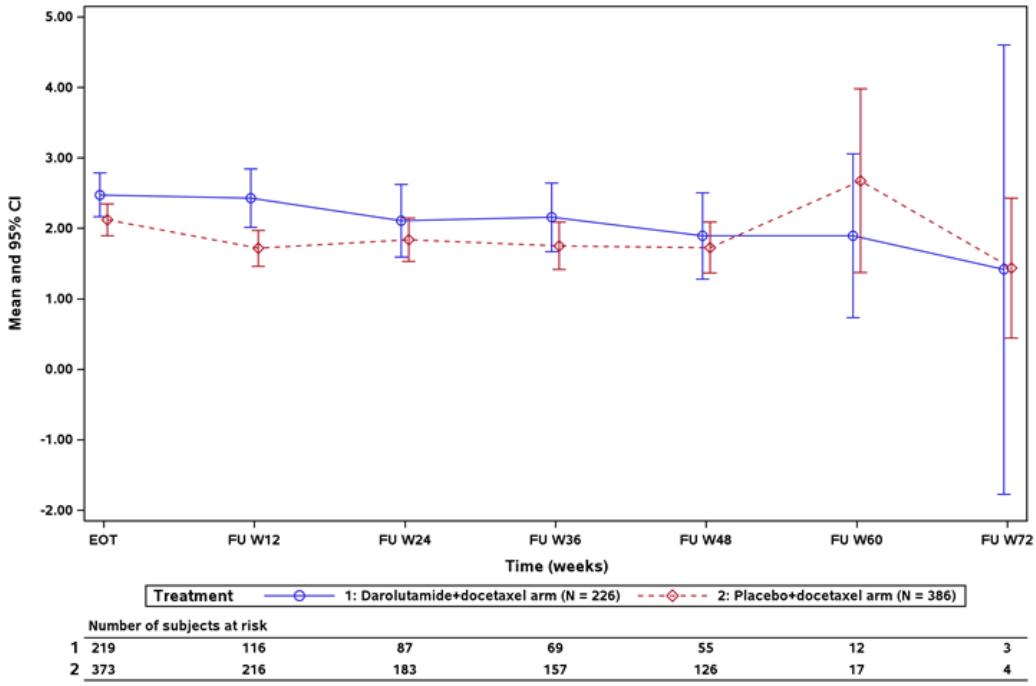
Figure 33 b: NCCN-FACT FPSI 17 questionnaire during follow-up period - means with 95% CI: Function and well-being subscale (FWB) Score (full analysis set)

BPI-SF questionnaire – Pain assessment



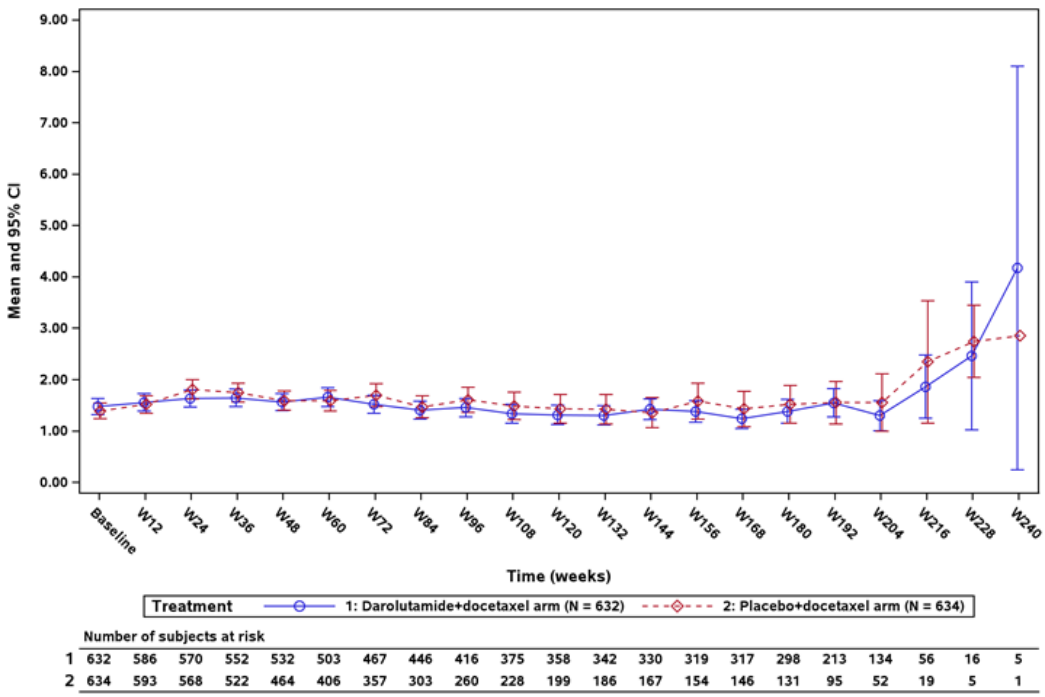
EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

Figure 34 a: BPI-SF questionnaire during treatment period - means with 95% CI: Pain Severity Score (full analysis set)



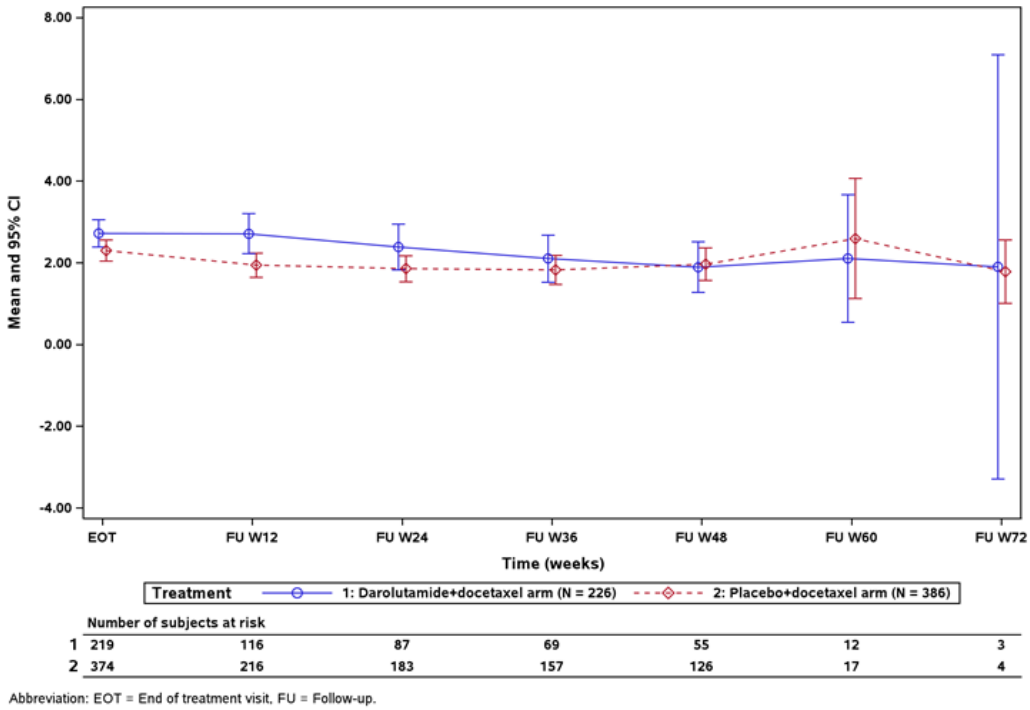
Abbreviation: EOT = End of treatment visit, FU = Follow-up.

Figure 30 b: BPI-SF questionnaire during follow-up period - means with 95% CI: Pain Severity Score (full analysis set)



EOT (End of treatment) visits are included by +/- 6 weeks-time window for the corresponding timepoints in this plot.

Figure 35 a: BPI-SF questionnaire during treatment period - means with 95% CI: Pain Interference Score (full analysis set)



Abbreviation: EOT = End of treatment visit, FU = Follow-up.

Figure 31 b: BPI-SF questionnaire during follow-up period - means with 95% CI: Pain Interference Score (full analysis set)

Table 44 : BPI-SF questionnaire - Time Adjusted AUC overall: summary statistics (full analysis set)

BPI-SF Parameter	Treatment group	n	Mean (SD)	Median	Min, Max
BPI-SF pain severity score	Darolutamide+docetaxel arm	618	1.555 (1.506)	1.134	0.00, 8.37
	Placebo+docetaxel arm	617	1.636 (1.533)	1.245	0.00, 8.86
BPI-SF pain interference score	Darolutamide+docetaxel arm	618	1.614 (1.617)	1.106	0.00, 8.24
	Placebo+docetaxel arm	617	1.727 (1.705)	1.167	0.00, 9.15

AUC was not calculated if baseline score was missing.

Table 45 : BPI-SF questionnaire - ANCOVA analysis of time adjusted AUC - descriptive Analysis: Mean difference (full analysis set)

BPI-SF Parameter	Treatment group	LS Mean	95 % confidence interval
Pain Severity Score	Darolutamide+docetaxel arm	1.57	[1.41;1.73]
	Placebo+docetaxel arm	1.65	[1.49;1.81]
	Difference	-0.08	[-0.22;0.05]
Pain Interference Score	Darolutamide+docetaxel arm	1.61	[1.43;1.78]
	Placebo+docetaxel arm	1.76	[1.59;1.93]
	Difference	-0.15	[-0.30;0.00]

AUC was not calculated if baseline score was missing.
Note: Patient level variability is a random effect. Treatment, score at baseline and IxRS stratification factors: extent of disease and ALP are the fixed effects in this linear mixed model.

Table 46 : BPI-SF questionnaire - ANCOVA analysis of time adjusted AUC - inferential Analysis: Treatment effect (full analysis set)

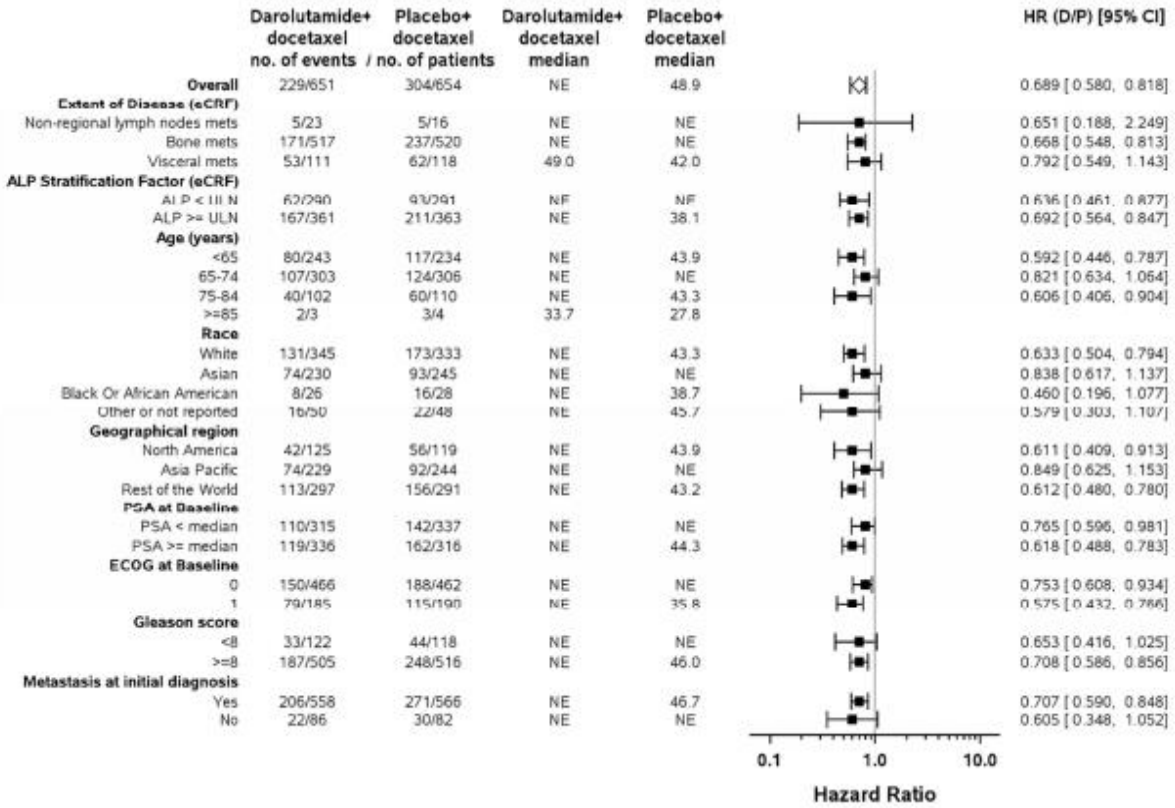
	Effect : Two-sided p-value			
BPI-SF Parameter	Treatment	Extent of disease*	ALP (< ULN vs. >= ULN)	Score at baseline
Pain Severity Score	0.2309	0.9567	0.3948	<.0001
Pain Interference Score	0.0436	0.9753	0.7796	<.0001

Note: * Extent of disease: Non-regional lymph nodes metastases only, Bone metastases with or without lymph node metastases, Visceral metastases with or without lymph node metastases or with or without bone metastases.
Note: Two-sided type I error of 5% p-value.
AUC was not calculated if baseline score was missing.
Note: Patient level variability is a random effect. Treatment, score at baseline and IxRS stratification factors: extent of disease and ALP are the fixed effects in this linear mixed model.

Ancillary analyses

Subgroup Analysis

Primary efficacy endpoint - Overall survival



Abbreviations: ALP=Alkaline phosphatase; CI=Confidence interval; D/P=Darolutamide+docetaxel arm / placebo+docetaxel arm; ECOG=Eastern Cooperative Oncology Group performance status; eCRF=Electronic case report form; FAS=Full analysis set; HR=Hazard ratio; mets=Metastases; NE=Not evaluable due to censored data; no.=number; PSA=Prostate-specific antigen; ULN=Upper limit of normal
A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm.
Hazard ratios and CIs were obtained from univariate analysis using Cox regression (unstratified). Medians were computed using Kaplan-Meier estimates.
No HR was calculated if <10 total events were observed within the subgroups across the treatment arms.
Extent of disease classification: Non-regional lymph node mets=M1a; Bone mets=M1b; Visceral mets=M1c

Figure 36: Subgroup analysis results of overall survival (FAS)

Sensitivity analyses

Table 47 : Sensitivity analyses of overall survival in Study 17777 (FAS)

Sensitivity analysis		Hazard ratio [a]: Darolutamide+docetaxel vs. Placebo+docetaxel [95% CI]	One-sided p-value from log-rank test
Analysis 1	Without including stratification factors in the model	0.689 [0.580; 0.818]	<0.0001
Analysis 2	Using stratification data from the eCRF	0.678 [0.571; 0.806]	<0.0001
Analysis 3 [b]	Using extent of disease stratification data according to central imaging review	0.678 [0.571; 0.805]	<0.0001

CI=Confidence interval; eCRF=Electronic case report form; FAS=Full analysis set

Note: Descriptive statistics and Kaplan-Meier survival curves were exactly the same as in the primary analysis.

a: A hazard ratio <1 indicates superiority of the darolutamide+docetaxel arm over the placebo+docetaxel arm. The hazard ratio and 95% CI were based on Cox regression model.

b:The stratification process in the Imaging Charter was set up such that in case of disagreement on the stratification group between central review and the site, the site re-evaluated the assessment with additional information from central review. Only in case of agreement could the patient be randomized. Nevertheless, there were discrepancies in 4 patients' stratification groups. A sensitivity analysis using stratification data according to central imaging review was performed to address the discrepancy.

Sensitivity analysis of time to CRPC: A sensitivity analysis was performed based on both central and local laboratory PSA and testosterone assessments. With 147 (22.6%) events in the darolutamide+docetaxel arm and 217 (33.2%) in the placebo+docetaxel arm, positive results in time to CRPC excluding PSA progression were observed in favour of the darolutamide+docetaxel arm, supporting the primary analysis (HR 0.463; 95% CI: 0.375; 0.572)

Additional Analysis

Table 48: Summary of subsequent life-prolonging systemic antineoplastic therapy for prostate cancer, by preferred drug name based on WHO-DD drug record number (FAS)

Preferred drug name(s) WHO-DD Version 2021SEP	Darolutamide+ docetaxel arm N=651 n (%)	Placebo+ docetaxel arm N=654 n (%)
Patients with subsequent life-prolonging systemic antineoplastic therapy	**179 (27.5%)**	**374 (57.2%)**
1 regimen	108/179 (60.3%)	221/374 (59.1%)
>1 regimen	71/179 (39.7%)	153/374 (40.9%)
Patients who entered Active or Survival follow-up [a]	**315/651 (48.4%)**	**495/654 (75.7%)**
Patients with subsequent life-prolonging systemic antineoplastic therapy	**179/315 (56.8%)**	**374/495 (75.6%)**
Abiraterone, abiraterone acetate	112/315 (35.6%)	232/495 (46.9%)
Enzalutamide	48/315 (15.2%)	136/495 (27.5%)
Cabazitaxel, cabazitaxel acetone	57/315 (18.1%)	89/495 (18.0%)
Docetaxel	46/315 (14.6%)	89/495 (18.0%)
Radium ra 223 dichloride	19/315 (6.0%)	34/495 (6.9%)
Sipuleucel-T	4/315 (1.3%)	10/495 (2.0%)
Lutetium (LU 177)	1/315 (0.3%)	6/495 (1.2%)
Apalutamide	2/315 (0.6%)	2/495 (0.4%)
Lutetium (177LU) PSMA-617	1/315 (0.3%)	1/495 (0.2%)

FAS=Full analysis set; N=Total number of patients (100%); n=Number of patients with event; WHO-DD=World Health Organization Drug Dictionary
A patient could receive more than one subsequent life-prolonging systemic antineoplastic medication. All medications summarized in this table were those administered after randomization.
The 7 patients who started life-prolonging systemic antineoplastic medications during the treatment period are included.
Preferred drug name was defined based on WHO-DD drug number, sequence #1 and sequence #2='001'.
Different preferred drug names listed under the same WHO-DD drug record number were combined.
Subsequent life-prolonging therapies for prostate cancer were defined as: abiraterone, apalutamide, enzalutamide, docetaxel, cabazitaxel, radium-223, sipuleucel-T, and lutetium-177.

Summary of main study

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

Table 49 : Summary of Efficacy for ARASENS

Title: "A randomized, double-blind, placebo-controlled Phase III study of darolutamide (ODM-201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer"		
Study identifier	Internal study number: 17777 Study name: ARASENS EudraCT number: 2015–002590–38 ClinicalTrials.gov identifier: NCT02799602	
Design	Multinational, randomized (1:1), double-blind, placebo-controlled, Phase 3 efficacy and safety study	
Hypothesis	Superiority of darolutamide+docetaxel over placebo+docetaxel in overall survival	
Treatment groups	Darolutamide+docetaxel arm	Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg. Docetaxel (75 mg/m^2 as an IV infusion) every 21 days for 6 cycles

			Concurrently with ADT Duration (overall time under treatment) median (min – max): 40.982 months (0.13 – 56.50 months) Number randomized: 651 patients [a]
	Placebo+docetaxel arm		Matching placebo twice daily with food. Docetaxel every 21 days for 6 cycles (75 mg/m^2 as an IV infusion) Concurrently with ADT Duration (overall time under treatment) median (min – max): 16.689 months (0.26 – 55.78 months) Number randomized: 654 patients [a]
Endpoints and definitions	**Primary:** Overall survival	OS	Time from randomization until death from any cause
	Secondary: Time to castration-resistant prostate cancer	Time to CRPC	Time from randomization to the occurrence of PSA progression, radiological progression by soft tissue and visceral lesions, or radiological progression by bone lesions
	Secondary: Time to pain progression	Time to PP	Time from randomization to pain progression. Pain progression was assessed by the initiation of short- or long-acting opioid use for pain and the BPI-SF questionnaire.
	Secondary: Symptomatic skeletal event-free survival	SSE-FS	Time from randomization to the first occurrence of an SSE or death from any cause, whichever came first. SSE was defined as EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention.
	Secondary: Time to first symptomatic skeletal event	Time to SSE	Time from randomization to the occurrence of the first SSE.
	Secondary: Time to initiation of subsequent systemic antineoplastic therapy	Time to 1st subsequent therapy	Time from randomization to start of the first subsequent systemic antineoplastic therapy for prostate cancer.
	Secondary: Time to worsening of disease-related physical symptoms	Time to worsening of symptoms	Time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire.
	Secondary: Time to initiation of opioid use for ≥7 consecutive days	Time to 1st opioid use for ≥7 days	Time from randomization to the date of first opioid use (for prostate cancer pain) for ≥7 consecutive days.

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (all randomized patients) Primary completion database cut-off date: 25 OCT 2021		
	Treatment group	Darolutamide +docetaxel arm	Placebo+ docetaxel arm
	Number of subjects	651	654
	OS	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.675
		[95% CI]	[0.568; 0.801]
		p-value [d]	<0.0001
	Time to CRPC	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.357
		[95% CI]	[0.302; 0.421]
		p-value [d]	<0.0001
	Time to PP	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.792
		[95% CI]	[0.660; 0.950]
		p-value [d]	0.0058
	SSE-FS	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.609
		[95% CI]	[0.516; 0.718]
		p-value [d]	<0.0001
	Time to SSE	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.712
		[95% CI]	[0.539; 0.940]
		p-value [d]	0.0081
	Time to 1st subsequent therapy	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.388
		[95% CI]	[0.328; 0.458]
		p-value [d]	<0.0001
	Time to worsening of symptoms	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	1.043
		[95% CI]	[0.894; 1.217]
		p-value [d]	0.7073
	Time to 1st opioid use for ≥7 days [e]	Comparison groups	Darolutamide+docetaxel vs Placebo+docetaxel
		Hazard ratio [c]	0.688
		[95% CI]	[0.523; 0.906]
		p-value [d,e]	0.0037 [e]

ADT=Androgen deprivation therapy; ALP=Alkaline phosphatase; BPI-SF=Brief pain inventory – short form; CI=Confidence interval; CRPC=Castration-resistant prostate cancer; EBRT=External beam radiation therapy; EudraCT=European Clinical Trials Database; FPFV=First patient's first visit; IV=Intravenous; M1a/M1b/M1c=classification of metastatic disease; max=Maximum; mHSPC=Metastatic hormone-sensitive prostate cancer; min=Minimum; NCCN-FACT-FPSI-17=National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy – Prostate Symptom Index 17-item questionnaire; OS =Overall survival; PP=Pain progression; PSA=Prostate-specific antigen; SSE=Symptomatic skeletal event; SSE-FS=Symptomatic skeletal event-free survival; ULN=Upper limit of normal

A=Value cannot be estimated due to censored data.

a: A total of 1306 patients were randomized. One patient was excluded from all analyses due to a Good Clinical Practice (GCP) violation. One patient randomized to and included in the placebo+docetaxel arm received darolutamide for 85 days.

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

c: A hazard ratio <1 indicates superiority of darolutamide+docetaxel over placebo+docetaxel. The hazard ratio and 95% CI were based on Cox regression model, stratified by extent of disease (M1a vs. M1b vs. M1c) and ALP (<ULN vs. ⩾ULN).

d: One-sided p-value from stratified log-rank test

e: The secondary endpoints were tested with a hierarchical gatekeeping procedure in the following order: Time to CRPC, Time to PP, SSE-FS, Time to SSE, Time to 1st subsequent therapy, Time to worsening symptoms, and Time to 1st opioid use for ⩾7 days. As Time to worsening symptoms did not reach the one-sided alpha significance threshold of 0.025 for this analysis, the secondary efficacy endpoint Time to 1st opioid use for ⩾7 days was not tested for significance and was considered exploratory; p-value is for descriptive purposes only.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The current application is based on the results of the pivotal study ARASENS (Study 17777). This was a Phase III, multinational, randomized (1:1), double-blind, placebo-controlled study evaluating darolutamide 600 mg BID orally in combination with 6 cycles of docetaxel in combination with ADT. Patients were randomised in a 1:1 ratio to receive either darolutamide or placebo, each combined with docetaxel. The use of docetaxel in combination with ADT as comparator is acceptable as recommended by ESMO in the treatment of mHSPC (Cancer of the prostate: ESMO Clinical Practice, Guidelines for diagnosis, treatment and follow-up, volume 31, 25 June 2020).

Considering the study design, the initially claimed indication has been modified to reflect that darolutamide is administered in combination not only with docetaxel but also with ADT.

Eligibility criteria are considered acceptable considering the claimed indication. It is noted that patients were included in the study regardless of disease volume. Patients were stratified at randomization by extent of disease (non-regional lymph node metastases only [M1a]; bones metastases with or without lymph node metastases [M1b]; visceral metastases with or without lymph node metastases or with or without bone metastases [M1c]) and by alkaline phosphatase (ALP), <ULN or ≥ULN at baseline. The addition of radiotherapy may be recommended for some patients according to current guidelines (i.e. patients with low volume disease). However, patients receiving treatment with radiotherapy were excluded from the study, which is acknowledged taking into account the available evidence at the time of study start. According to the protocol, palliative radiation therapy or surgical intervention as needed were allowed during study treatment. Treatment with bisphosphonates and denosumab was also allowed.

The dose of darolutamide used in ARASENS study is the 600 mg bd tablet formulation in combination with docetaxel (75 mg/m^2 for 6 cycles). This dose showed a statistically significant and clinically meaningful efficacy benefit for mHSPC patients. The data indicate that darolutamide (600 bd) plus docetaxel has an acceptable tolerability profile when administered in the proposed target patient population. This choice of dose was supported by safety and PK data, exposure-response analyses, and exposure-safety analysis.

The primary objective of this study was to demonstrate superiority of darolutamide in combination with docetaxel over placebo in combination with docetaxel in OS. The secondary objectives were to evaluate the time to castration-resistant prostate cancer (CRPC), the time to pain progression, symptomatic skeletal event-free survival (SSE-FS), the time to first symptomatic skeletal event (SSE), the time to

initiation of subsequent systemic antineoplastic therapy, the time to worsening of disease-related physical symptoms, the time to initiation of opioid use for ≥7 consecutive days, and to characterize the safety of darolutamide in combination with docetaxel in mHSPC patients. Overall, the study design is considered acceptable. The Applicant has mostly followed the CHMP scientific advice except for the suggestion to add other primary endpoints (rPFS or Time to castrate resistance) considering OS could be confounded by further treatment lines given the disease stage. The sponsor did not add any further primary endpoints but changed the hierarchy of secondary endpoints by placing Time to castrate resistance first which is acceptable.

The sample size calculations were acceptable. The targeted treatment effect on OS (HR=0.75) was considered "meaningful and clinically relevant" (EMA/CHMP/SAWP/596563/2015). The randomisation process and associated stratification factors are appropriate.

Twenty-three patients (10 [1.5%] in the darolutamide arm and 13 patients [2.0%] in the placebo arm) never received docetaxel. According to the MAH, after randomization and start of study drug, they were no longer considered to be eligible to receive concomitant docetaxel within 6 weeks after start of study drug. Since numbers were low and balanced between treatment arms it is not considered that this may have impacted the results.

A relatively large proportion of patients had premature emergency unblinding performed at the study site by the investigator (89 patients in total, 26 darolutamide + docetaxel + ADT and 63 placebo+docetaxel). Investigators were unblinding patients to inform the choice of subsequent therapy which was not allowed per protocol. The MAH clarified that premature unblinding was limited to the investigator and patient, and that study team members remained blinded to treatment allocation until the formal study unblinding at the time of analyses. The impact and potential bias induced by premature unblinding on subsequent patient measurements have been discussed and post-hoc analyses have been provided for two endpoints considered to be most likely influenced by premature unblinding: time to pain progression and time to worsening of physical disease-related symptoms. The MAH also clarified that 18 patients (2.8%) in the darolutamide+docetaxel arm and 43 (6.6%) in the placebo+docetaxel arm received at least 1 subsequent systemic antineoplastic therapy after premature unblinding. In general, bias cannot be completely ruled out in the presence of premature unblinding. However, the additional information and post-hoc analyses performed (data not shown) provided some reassurance on the potential impact on study results.

For the secondary endpoint of time to castration-resistant prostate cancer, it is noted that data following two or more consecutive missing assessments or following the start of subsequent therapy are being censored at the last assessment date before these occurrences. The MAH was requested to perform a supplemental analysis of time to castration-resistant prostate cancer following a treatment policy strategy for these intercurrent events (IEs) (start of subsequent therapy, and ≥2 consecutive missing assessment), i.e. without censoring data in these situations, and making use of following observations instead. The results (not shown) were consistent with the main analysis results.

The statistical methods for analysing primary and secondary endpoints (stratified log-rank test and Cox model) are standard and adequate for these time to event variables.

There were several changes to the planned analyses, including the removal of the second interim analysis, the introduction of gatekeeping procedure in the SAP, and the exclusion of the patient data with a critical GCP violation. Given the double-blind nature of the study, the review of the amendments is not thought to have affected the overall interpretation of the study results.

Regarding protocol deviations, frequency of important protocol deviations was similar between treatment arms (73.3% and 73.9% in the darolutamide and placebo arm, respectively). The most commonly

reported were related to procedure deviations (56.8% vs 57.0%) and treatment deviations (36.4% vs 35.5%). Of the total number of protocol deviations, 15.8% and 12.1%, in each treatment arms, respectively, were related to COVID-19 pandemic. However, even if numbers were comparable between treatment arms, the rate was considered high. According to the MAH a broad definition of "important protocol deviations" was used in the study, which somehow would explain the high rates of protocol deviations reported, in addition to those related to COVID-19 pandemic. Detailed information on the causes of procedure and treatment deviations was also submitted and no major differences were observed between treatment arms.

Efficacy data and additional analyses

Baseline data

Overall, the baseline demographic and baseline patient and disease characteristics of FAS were generally well balanced between the 2 treatment arms. The majority of patients included in the study had high volume disease (77%), applying the CHAARTED criteria. Further, according to inclusion/exclusion criteria, patients with brain metastases were allowed to enter the study but there were no patients with (known) brain metastasis enrolled in the study.

Docetaxel could be given with prednisone/prednisolone. According to the information provided by the MAH, 18.6% and 22% of patients in the darolutamide and placebo arms, respectively, received prednisolone while 23.2% and 18.5%, respectively, received prednisone. There were also around 7.5% of patients that received methylprednisolone. Further, around 80% of patients received dexamethasone. Dexamethasone was given as a premedication according to the above definition in 45.9% (299/651) of patients in the darolutamide+docetaxel arm and in 49.4% (323/654) in the placebo+docetaxel arm. Almost 235 patients in the darolutamide+docetaxel arm and 219 patients in the placebo+docetaxel arm received dexamethasone not used as premedication according to the predefined time window: a start date within 3 days prior to any docetaxel cycle treatment (Day-3), and a stop date within 5 days after each docetaxel cycle treatment date (Day+5). The reason why majority of the patients had the reason 'Other' was that there was no specific field in the eCRF to capture prophylactic use and the data was collected as free text.

The majority of patients (85%) had not received prior surgical or radiation treatment. Around 25% of patients received concomitant treatment with bisphosphonates or denosumab.

Primary endpoint

The primary efficacy analysis in support of this application was performed at the data cut-off of 25-oct-2021.

With a total of 553 OS events: 229 deaths (35.2% of patients) in the darolutamide + docetaxel + ADT arm; 304 deaths (46.5% of patients) in the placebo + docetaxel + ADT arm, ARASENS study met its primary endpoint with a statistically significant improvement of OS in the darolutamide + docetaxel + ADT arm compared to placebo + docetaxel + ADT. The addition of darolutamide to backbone docetaxel + ADT decreased the risk of death of 32.5% compared to the placebo arm (HR: 0.675; 95% CI: [0.568; 0.801], p<0.0001) which is considered clinically relevant for the target population. Median OS was not reached in the darolutamide + docetaxel + ADT arm (95% CI: [A; A]) and was 48.9 months in the placebo + docetaxel + ADT arm (95% CI: [44.4; A]). However, median OS in the control arm was lower than expected at the time of the estimation of the sample size and lower than the reported in studies STAMPEDE and CHAARTED (62 months and 57.6 months, respectively). Further, in the study PEACE-

1[1], in de novo metastatic prostate cancer patients, median OS in the docetaxel plus ADT arm was of around 53 months. In this study, radiotherapy was allowed. The MAH provided supporting evidence to justify the difference observed of median OS between studies (CHAARTED, STAMPEDE and PEACE-1). The most likely cause of this observed difference, was the difference in clinical prognostic factors between the patients. Indeed, it is well known that Gleason score >8 as well as a diagnosis of de novo mHSPC or the presence of visceral metastases are factors of worse prognosis in prostate cancer.

A high number of censored patients was reported in both arms, representing almost 60% of the FAS population, with 64.8% in the darolutamide arm and 53.5% in the placebo arm. The provided description of the reasons for censoring, provided reassurance that the censorships were balanced between both arms throughout the study conduct. Likewise, a sensitivity analysis of the primary endpoint imputing the use of prohibited medication as event was consistent with the primary analysis.

Secondary endpoints

The start of a **new systemic antineoplastic therapy** was reported for 33.6% of patients in the darolutamide + docetaxel + ADT arm compared with 60.4% in the placebo + docetaxel + ADT arm. There was a statistically significant and clinically meaningful improvement in time to first systemic therapy (TFST) associated with darolutamide + docetaxel + ADT vs the control arm (HR of 0.388, 95% CI: [0.328; 0.458]; p<0.0001).

Given the stage of the disease, OS could be confounded by further treatment lines. The use of subsequent therapies known to have impact on patient´s survival was almost 1.33-fold higher in the placebo arm, which is in line with what can be expected based on primary results. However, the magnitude of the impact that subsequent therapies have in OS results cannot be complete elucidated.

Time to castrate resistance was considered the most relevant secondary endpoint and was defined as the time to PSA progression (i.e. ≥25% increase and an absolute increase ≥2 ng/ml from the nadir) with serum testosterone being at castrate level <0.50 ng/mL, or the time to radiological progression by soft tissue/visceral lesions or by bone lesions whichever occurs first. CRPC was documented for 225 (34.6%) patients in the darolutamide + docetaxel + ADT arm and 391 (59.8%) patients in the placebo + docetaxel + ADT arm. Of the patients who progressed to CRPC, the first progression event observed was mostly PSA progression for 121/225 patients (53.8%) in the darolutamide + docetaxel + ADT arm compared with 289/391 patients (73.9%) in the placebo + docetaxel + ADT arm. A statistically significant prolonged time to CRPC was observed for patients in the darolutamide + docetaxel + ADT arm compared with the placebo + docetaxel + ADT arm, with an HR of 0.357 (95% CI: [0.302; 0.421]); p<0.0001. The median time to CRPC was not reached (95% CI: [A; A]) in the darolutamide + docetaxel + ADT arm and was 19.1 months (95% CI: [16.5; 21.8]) in the placebo + docetaxel + ADT arm.

This delay in the time to CRPC was mainly based on PSA progression, which was in fact the main (first) event observed in both treatment arms. However, no apparent differences were observed between treatment arms in terms of radiological progression by bone or visceral lesions. As mentioned, rPFS was not included as secondary endpoint in the study, which would have provided information about the effect of darolutamide in delaying radiological disease progression.

The assessment of PSA progression was questioned taking into account that only 53% of patients had testosterone castrate levels at baseline. At Visit 2 (Week 12) 93.7% of patients had castrate levels of testosterone. Considering at Visit 2 most patients were already on castrated levels it is presumed that no events of PSA progression had been reported for the vast majority of patients. Since testosterone at castrate levels was a necessary condition for a PSA progression event, the MAH clarified that patients

[1] Fizazi K et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2022 Apr 30;399(10336):1695-1707.

who did not have a testosterone castrate level did not qualify for a PSA progression event. Among the 76 (6.3%) remaining patients with non-castrate testosterone level at Visit 2, 22 patients fulfilled the criteria for PSA progression at a subsequent and confirmation visit. There were 54 patients who did not fulfil the criteria and therefore were not evaluable for PSA progression but were assessed for radiological progression. Of these 54 patients 13 had radiological progression. Thus, in total, of the 76 patients, 35 experienced an event.

As this variation proposes the use of darolutamide as an add-on to one of the standard of care, the quality of life of patients is important in the evaluation of the claimed indication. Main secondary endpoints which indirectly reflect the quality of life of patients were: Time to pain progression; SSE-FS; Time to first SSE; Time to initiation of subsequent systemic antineoplastic therapy; Time to worsening of disease-related physical symptoms based on functional assessment of cancer therapy; Time to initiation of opioid use for ≥7 consecutive days.

The time to first symptomatic skeletal events in the study and the time to initiation of opioid use were considered clinically relevant in this context.

A statistically significant delay in time to pain progression was observed in favour of the experimental arm (HR 0.792; 95% CI: [0.660, 0.950]), with 34.1% events in the darolutamide arm and 37.9% in the placebo arm. Median time to pain progression was not reached in the darolutamide arm and was of 27.5 months in the placebo arm. Sensitivity analyses were consistent. Approximately 71.5% of patients in the study were taking concomitant analgesics. SSEs were reported in 14.6% of patients in the darolutamide + docetaxel + ADT arm compared with 16.5% in the placebo + docetaxel + ADT arm with a numerical improvement (i.e. a delay) of **time to first SSE** for patients in the darolutamide + docetaxel + ADT arm, with an HR of 0.712 (95% CI: [0.539; 0.940]); p=0.0081. The median time to first SSE was not reached (95% CI: [A; A]) in either treatment arm. The majority of the first SSEs were External beam radiation therapy to relieve skeletal symptoms, reported for 63.2% of patients with an SSE in the darolutamide + docetaxel + ADT arm and 82.4% of patients with an SSE in the placebo + docetaxel + arm.

Worsening of disease-related physical symptoms was observed for 53.9% of patients in the darolutamide + docetaxel + ADT arm and 47.1% of patients in the placebo + docetaxel + ADT arm. There was no significant difference in **time to worsening of disease-related physical symptoms** between the treatment arms (HR=1.043; 95% CI: [0.894, 1.217]; p=0.7073). The median time to worsening of disease-related physical symptoms was 19.3 months (95% CI: [13.8, 24.8]) in the darolutamide + docetaxel + ADT arm and 19.4 months (95% CI: [15.4, 27.6]) in the placebo + docetaxel + ADT arm.

Since time to worsening of disease-related physical symptoms was not statistically significant, the results of the secondary endpoint **time to initiation of opioid use** were considered exploratory. It is to be noted that 14.1% of patients in the darolutamide + docetaxel + ADT arm and 17.9% in the placebo + docetaxel + ADT arm had initiated opioid treatment for cancer pain for ≥7 consecutive days. The time to first opioid use for ≥7 consecutive days showed an advantage in favour of the darolutamide + docetaxel + ADT arm, with an HR of 0.688 (95% CI: [0.523; 0.906]); p=0.0037.

Findings from secondary efficacy analyses all showed statistically significant results in favour of darolutamide + docetaxel + ADT arm except for the Time to worsening of disease-related physical symptoms based on the NCCN–FACT-FPSI-17 questionnaire.

Exploratory endpoints

Additional **exploratory endpoints** also favoured darolutamide + docetaxel + ADT arm compared to placebo + docetaxel.

Baseline PSA values were comparable between the treatment arms (median 30.30 ng/mL in the darolutamide + docetaxel + ADT arm and 24.20 ng/mL in the placebo + docetaxel + ADT arm). Treatment with darolutamide in combination with docetaxel resulted in a longer time to PSA progression than placebo in combination with docetaxel, with an HR of 0.255 (95% CI: [0.208; 0.313]); p<0.0001.

The majority of the patients in the darolutamide + docetaxel + ADT arm (88.6%) and in the placebo + docetaxel + ADT arm (68.7%) had a maximum PSA decline of ≥90% from baseline at any time on study treatment.

Patients in the darolutamide + docetaxel + ADT arm showed a significantly higher relative PSA response rate of ≥90% reduction from baseline at 12 months after randomization than patients in the placebo + docetaxel + ADT arm, 84.3% vs. 57.5%, respectively (difference=26.82%, 95% CI: [22.11; 31.53], p<0.0001). Both absolute PSA response rates (PSA level <0.2 ng/mL) and relative PSA response rates (≥90% reduction in PSA from baseline) were higher in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm at all evaluated time points.

Concerning quality of life (QoL), the results indicated that health-related QoL was maintained while on treatment in patients in both treatment arms. At baseline (i.e., Screening or Visit 1/Day 1), the BPI-SF pain interference and pain severity 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, and there were no clinically meaningful differences (MID=2 points) between the treatment arms.

Subgroups analysis

The different subgroup analyses according to tumour volume (high and low tumour volume) showed a favourable benefit in overall survival and other efficacy outcomes (time to castration-resistant prostate cancer, symptomatic skeletal event-free survival, time to initiation of subsequent systemic antineoplastic therapy) with no major differences were observed regarding burden of disease.

2.4.4. Conclusions on the clinical efficacy

Despite therapeutic advances in recent years in the treatment of prostate cancer, the arsenal of treatment in mHSPC setting remains limited.

ARASENS study met its primary endpoint with a statistically significant improvement of OS in the darolutamide + docetaxel + ADT arm compared to placebo + docetaxel. ARASENS study demonstrated a reduction of the risk of death of 32.5% in the darolutamide + docetaxel + ADT arm compared to the placebo + docetaxel + ADT arm (HR: 0.675; 95% CI: [0.568; 0.801]), and the log-rank test was statistically significant with a one-sided p<0.0001.

Findings from secondary efficacy analyses all showed statistically significant results in favour of darolutamide + docetaxel + ADT arm except for the Time to worsening of disease-related physical symptoms based on the NCCN–FACT-FPSI-17 questionnaire. The combination darolutamide + docetaxel, in the ARASENS study, significantly reduced the onset of castration-resistant disease, prolonged the time to the first SSE, and the time to subsequent systemic antineoplastic therapy.

2.5. Clinical safety

Introduction

The evidence for the clinical safety of darolutamide in combination with docetaxel for the treatment of mHSPC is based on the data from the **pivotal Study 17777 (ARASENS)** in patients with mHSPC

(n=1302) from start of the study (30 NOV 2016) until the database cut-off date for the primary completion analysis (25 OCT 2021).

Safety data were also derived from the following sources:

- Integrated analysis of safety from completed uncontrolled Phase 1/2 darolutamide studies in patients with **mCRPC** (mCRPC pool) comprising Study 17829 (ARADES) [including extension Study 18035 (ARADES-EXT)], Study 17830 (ARAFOR), and Study 17719 (n=173).
- Integrated analysis of safety from completed Phase 1 single dose darolutamide studies in **non-cancer subjects** (non-cancer subject pool) comprising Studies 17721, 17726, 17831, and 18426. No new multiple dose darolutamide studies were conducted since the submission of the initial dossier, therefore, "non-cancer subject pool" refers to the updated integrated analysis of the single dose studies in this SCS (n=80).

In addition, the summaries of deaths and serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs) leading to treatment discontinuation were provided from the ongoing Phase 3 Study 21140 (ARANOTE) in mHSPC patients, and for the ongoing roll-over Study 20321.

Analysis sets

All safety evaluations are presented for the safety analysis set (SAF), defined as:

- Phase 3 Study 17777 (ARASENS): all randomized patients who received at least one dose of study drug (darolutamide or placebo), except for cases with critical GCP violations. Patients were included in the analyses according to the treatment they actually received. Patients were included in the darolutamide + docetaxel + ADT arm if they had received any dose of darolutamide.
- Integrated safety analyses in mCRPC patients (mCRPC pool) and in non-cancer subjects (non-cancer subject pool): all patients and subjects, respectively, who received at least one dose of study treatment.

Table 50 Overview of clinical studies included in the summary of clinical safety

Study no. and Phase	Number of study centers and locations	Study period and study reports	Study design and type of control	Primary and secondary objectives	Study population	Treated patients / exposed subjects as of 25 OCT 2021	Treatment and dose	Demographics Gender Median age in years (range) Race	Safety evaluations included in the submission	Deaths / SAEs / AEs leading to study treatment discontinuation / Any AE [a]
17777 ARASENS Phase 3	301 centers in Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, mainland China, Finland, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Poland, Russian Federation, South Korea, Spain, Sweden, Taiwan, UK, US	FPFV 30 NOV 2016 Primary completion analysis: 25 OCT 2021 Module 5.3.5.1, Report PH-42024	Randomized (1:1), double-blind, placebo-controlled	Primary: Superiority in OS of darolutamide in combination with docetaxel over placebo in combination with docetaxel. Secondary: time to CRPC, time to pain progression, SSE-FS, time to first SSE, time to initiation of subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms, the time to initiation of opioid use for ≥7 consecutive days, safety	Patients with mHSPC	Total: **1302** [b] Darolutamide+ docetaxel arm: 652 Placebo+ docetaxel arm: 650	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg, or placebo in combination with 6 cycles of docetaxel at 75 mg/m² as an IV infusion every 21 days Concurrently with ADT	**Darolutamide+ docetaxel arm:** [c] 651 male 67.0 years (41–89 years) White: 53.0% Black or African American: 4.0% Asian: 35.3% Other: 1.1% Not reported: 6.6% **Placebo+docetaxel arm:** [c] 654 male 67.0 years (42–86 years) White: 50.9% Black or African American: 4.3% Asian: 37.5% Other: 0.3% Not reported: 7.0%	Extent of exposure TEAEs TEAEs leading to discontinuation TEAEs leading to dose modification TESAEs Deaths Special topics of grouped AE terms Subgroup analysis of TEAEs Laboratory parameters Vital signs ECG	Darolutamide+docetaxel arm vs. placebo+docetaxel arm **Deaths**: Grade 5 TEAEs: 27 patients (4.1%) vs. 26 patients (4.0%) Overall : 229 deaths (35.1%) vs. 304 deaths (46.8%) **TESAEs**: 40 patients (6.1%) vs. 39 patients (6.0%) **TEAEs leading to discontinuation of study drug**: 88 patients (13.5%) vs. 69 patients (10.6%) **Any TEAE**: 649 patients (99.5%) vs. 643 patients (98.9%)

Study no. and Phase	Number of study centers and locations	Study period and study reports	Study design and type of control	Primary and secondary objectives	Study population	Treated patients / exposed subjects as of 25 OCT 2021	Treatment and dose	Demographics Gender Median age in years (range) Race	Safety evaluations included in the submission	Deaths / SAEs / AEs leading to study treatment discontinuation / Any AE [a]
17830 ARAFOR (3104003) Phase 1	9 centers in Finland, France, Latvia	FPFV 14 MAR 2013 30 APR 2017 cut-off (6 patients ongoing with treatment) Module 5.3.1.1, Report R-9789 LPLV 18 DEC 2020 Module 5.3.1.1, Report Addendum R-13926	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	Darolutamide 600 mg PK Component: single dose orally with and w/o food Extension Component: multiple dose BID orally Concurrently with ADT (both components)	30 male 68.0 years (54–86 years) Caucasian: 30 patients (100%)	Extent of exposure TEAEs TESAEs Deaths Laboratory parameters Vital signs ECG	<u>R-9789</u> **Deaths:** Grade 5 TEAE: 1 patient (3.3%) Overall: 3 deaths **TESAEs:** 11 patients (36.7%) **TEAEs leading to discontinuation:** 3 patients (10.0%) [d] **Any TEAE:** 23 patients (76.7%) <u>**Addendum R-13926**</u> **TESAEs:** 2 patients

Study no. and Phase	Number of study centers and locations	Study period and study reports	Study design and type of control	Primary and secondary objectives	Study population	Treated patients / exposed subjects as of 25 OCT 2021	Treatment and dose	Demographics Gender Median age in years (range) Race	Safety evaluations included in the submission	Deaths / SAEs / AEs leading to study treatment discontinuation / Any AE [a]
17829 ARADES (3104001) Phase 1/2	23 centers in Czech Republic, Estonia, Finland, France, UK, US	FPFV 28 MAR 2011 LPLV 09 JUL 2013 Module 5.3.3.2, Report R-9584	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 darolutamide 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 BID orally with food Phase 2: Darolutamide 100 mg 200 mg 700 mg BID orally with food Concurrently with ADT (both phases)	134 male 69.0 years (Ph 1) 69.5 years (Ph 2) (53–89 years) Caucasian: 128 patients (95.5%) Black: 5 patients (3.7%) Asian: 1 patient (0.7%)	Extent of exposure TEAEs TESAEs Deaths Laboratory parameters Vital signs ECG	**Deaths:** Grade 5 TEAE in 2 patients (1.5%) during treatment period Grade 5 TEAE in 2 patients (1.5%) during post-treatment period Overall: 5 deaths **TESAEs:** 13 patients (9.7%) **TEAEs leading to discontinuation:** 5 patients (3.7%) **Any TEAE:** 117 patients (87.3%)
18035 [e] ARADES-EXT (3104002) Phase 2	17 centers in Czech Republic, Estonia, Finland, France, UK, US	FPFV 30 JUN 2011 LPLV 21 OCT 2015 Module 5.3.5.2, Report R-11102	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	76 male 68.0 years (55–83 years) Caucasian: 74 patients (97.4%) Black: 1 patient (1.3%) Asian: 1 patient (1.3%)	Extent of exposure TEAEs TESAEs Deaths Laboratory parameters Vital signs ECG	**Deaths:** Grade 5 TEAE in 1 patient (1.3%) **TESAEs:** 19 patients (25.0%) **TEAEs leading to discontinuation:** 3 patients (3.9%) **Any TEAE:** 76 patients (100%)
20321 (ROS) Phase 3	Argentina, Australia, Austria, Belarus, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Japan, Latvia, Lithuania, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, South Korea; Spain, Sweden, Taiwan, Turkey, Ukraine, UK, US	FPFV 20 OCT 2020 Ongoing Primary completion not reached	Open-label, single arm, ROS	Primary: Continuation of darolutamide treatment and evaluation of safety	Patients with nmCRPC (from Study 17712) Patients with mCRPC (from Study 17830)	Total **410** [f] 409 patients (from Study 17712) 1 patient (from Study 17830)	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg, or placebo Concurrently with ADT	NA primary completion not reached	Deaths SAEs AEs leading to discontinuation	**Deaths:** [f] 8 deaths **SAEs:** [f] 38 patients **AEs leading to discontinuation:** [f] 7 patients
21140 ARANOTE Phase 3	Australia, Brazil, Canada, Chile, mainland China, India, Latvia, Lithuania, New Zealand, Peru, Russian Federation, South Africa, Spain, Taiwan, Ukraine	FPFV 23 FEB 2021 Ongoing Primary completion not reached	Open-label, randomized, double-blind, placebo-controlled, multicenter	Primary: Superiority of darolutamide + ADT over placebo + ADT in rPFS	Patients with mHSPC	119 [f]	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg, or placebo Concurrently with ADT	NA (primary completion not reached)	Deaths SAEs AEs leading to discontinuation	

Abbreviations: ADT=Androgen deprivation therapy; AE=Adverse event; BID=Twice daily; 14C=Carbon-14 (radiocarbon); CBF=Cerebral blood flow; CRPC=Castration-resistant prostate cancer; CYP=Cytochrome P450; DLT=Dose limiting toxicity; ECG=Electrocardiogram; FPFV=First patient first visit; FSFV=First subject first visit; HI=Hepatic impairment; IV=Intravenous; LPLV=Last patient last visit; LSLV=Last subject last visit; mCRPC=Metastatic castration-resistant prostate cancer; mHSPC=Metastatic hormone-sensitive prostate cancer; MTD=Maximum tolerated dose;

NA=Not available; nmCRPC=Non-metastatic castration-resistant prostate cancer; no.=Number; OS=Overall survival; Ph=Phase; PK=Pharmacokinetics, pharmacokinetic;
PV=Pharmacovigilance; RI=Renal impairment; ROS=Roll-over study; rPFS=Radiological progression-free survival; SAE=Serious adverse event; SSE=Symptomatic skeletal event; SSEFS=
Symptomatic skeletal event-free survival; TEAE=Treatment-emergent adverse event; TESAE=Treatment-emergent serious adverse event; UK=United Kingdom; US=United States of
America; w/o=Without
a: Only AEs occurring during study treatment (from first to last dose of study treatment) are included for study 17829. AEs occurring from start of study treatment until end-of-study visit are included
for studies 18035, 17830 and 17831. For all other completed studies, AEs occurring after start of study treatment until 30 days after the last study drug intake are presented.
b: There were 299 patients in the darolutamide+docetaxel arm and 125 in the placebo+docetaxel arm ongoing with treatment at the time of the database cut-off date for the primary completion
analysis of Study 17777 (25 OCT 2021).
c: Demographics data are for the full analysis set, including 651 patients in the darolutamide+docetaxel arm and 654 patients in the placebo+docetaxel arm.
d: Excluding 1 death leading to discontinuation.
e: In the integrated safety analysis, the data from study 18035 (long-term safety follow-up of 76 patients who continued treatment after the 12-week treatment period of study 17829) are pooled with
the safety data from study 17829.

- ***Patient exposure***

Darolutamide exposure

A summary of study drug exposure in Study 17777 until the database cut-off date for the primary completion analysis (25 OCT 2021) is presented in the table below.

Table 51 Study drug exposure in Study 17777 (SAF)

	Darolutamide+ docetaxel arm N=652	Placebo+ docetaxel arm N=650
Overall time under treatment (months) [a]		
Mean (StD)	31.853 (16.758)	22.188 (15.349)
Min, Max	0.13, 56.50	0.26, 55.78
Median	40.982	16.689
Categories (months), n (%) [a]		
0 – 3	34 (5.2%)	23 (3.5%)
>3 – ≤6	22 (3.4%)	53 (8.2%)
>6 – ≤9	33 (5.1%)	71 (10.9%)
>9 – ≤12	26 (4.0%)	82 (12.6%)
>12 – ≤18	69 (10.6%)	118 (18.2%)
>18 – ≤24	57 (8.7%)	60 (9.2%)
>24 – ≤30	34 (5.2%)	44 (6.8%)
>30 – ≤36	31 (4.8%)	33 (5.1%)
>36 – ≤42	35 (5.4%)	34 (5.2%)
>42 – ≤48	206 (31.6%)	94 (14.5%)
>48	105 (16.1%)	38 (5.8%)
Average daily dose (mg/day) [b]		
Mean (StD)	1176.712 (96.585)	1187.563 (65.658)
Min, Max	605.61, 1200.87	615.75, 1204.36
Median	1200.000	1200.000
Percent of planned dose [c]		
Mean (StD)	97.239 (9.276)	98.459 (6.119)
Min, Max	32.14, 100.07	48.40, 100.36
Median	100.000	100.000

Abbreviations: Max=Maximum; Min=Minimum; N=Total number of patients (100%); n=Number of patients within category; SAF=Safety analysis set; StD=Standard deviation
a: Overall time under treatment (months)=(day of last dose of study drug minus day of first dose of study drug +1)/30.44. Overall time includes dose interruptions and dose delays.
b: Average daily dose received = total amount of dose/number of days with intake >0.
If patient took both darolutamide and placebo, the placebo dosages are not included.
c: Percent of planned dose received incorporates treatment interruptions and dose reductions into the calculation.

After the last dose of docetaxel, patients continued on study drug treatment for a median time of 36.9 months in the darolutamide + docetaxel + ADT arm (n=642) and 13.1 months in the placebo + docetaxel + ADT arm (n=637).

Two cases of darolutamide overdose were reported, both with an actual total daily dose of 2400 mg for 1 day only. Following the overdose, no TEAEs were reported for either patient.

Docetaxel exposure

In Study 17777, docetaxel was administered at a dose of 75 mg/m^2 as an IV infusion every 21 days for 6 cycles, starting within 6 weeks after the start of study drug. A summary of docetaxel exposure in Study 17777 until the database cut-off date for the primary completion analysis is presented in the table below.

Table 52 Docetaxel exposure in Study 17777 (SAF)

	Darolutamide+ docetaxel arm N=652	Placebo+ docetaxel arm N=650
Number of patients with total number of cycles, n (%)		
0 (never received docetaxel)	10 (1.5%)	13 (2.0%)
1	20 (3.1%)	16 (2.5%)
2	14 (2.1%)	14 (2.2%)
3	14 (2.1%)	7 (1.1%)
4	12 (1.8%)	17 (2.6%)
5	11 (1.7%)	27 (4.2%)
6	571 (87.6%)	556 (85.5%)
Total number of cycles		
N	642	637
Mean (StD)	5.637 (1.134)	5.658 (1.055)
Min, Max	1.00, 6.00	1.00, 6.00
Median	6.000	6.000
Average cycle dose received (mg)		
N	642	637
Mean (StD)	138.497 (18.604)	139.055 (19.057)
Min, Max	82.96, 195.00	65.76, 206.00
Median	140.000	139.667
Percent of planned dose [a]		
N	638	635
Mean (StD)	96.039 (6.312)	95.843 (6.587)
Min, Max	72.78, 109.90	51.78, 105.39
Median	98.567	98.485
Missing (n)	14	15

Abbreviations: Max=Maximum; Min=Minimum; N=Total number of patients (100%); n=Number of patients within category; SAF=Safety analysis set; StD=Standard deviation

a: Percent of planned dose received incorporates treatment interruptions and dose reductions into the calculation.

Most patients in both treatment arms received at least 1 dose of docetaxel within 6 weeks after the first dose of darolutamide or placebo. There were 10 patients (1.5%) in the darolutamide + docetaxel + ADT arm and 13 patients (2.0%) in the placebo + docetaxel + ADT arm who never received docetaxel. These patients were initially assessed by the investigator to be candidates for ADT and docetaxel. After randomization and start of study drug, they were no longer considered to be eligible to receive concomitant docetaxel within 6 weeks after start of study drug.

Disposition

- Study 17777

A summary of patient disposition in Study 17777 as of the database cut-off date for the primary completion analysis (25 OCT 2021) is presented in **Table *53*** by treatment arm. Note: the end of treatment was defined as the day of the last dose of study drug (darolutamide or placebo).

Table 53 Patient disposition at the time of database cut-off date in Study 17777 (FAS)

Number of patients (%)	Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Randomized [a] (N=1305; included in FAS)	651 (100.0%)	654 (100.0%)
Study drug never administered	0	3 (0.5%)
Started treatment (N=1302; included in SAF [b])	651 (100.0%)	651 (99.5%)
Discontinued study treatment	352 (54.1%)	526 (80.4%)
Primary reason:		
Progressive disease - clinical progression	127 (19.5%)	272 (41.6%)
Progressive disease - radiological progression	84 (12.9%)	132 (20.2%)
Adverse event not associated with clinical disease progression	48 (7.4%)	27 (4.1%)
Withdrawal by patient	25 (3.8%)	35 (5.4%)
Adverse event associated with clinical disease progression	24 (3.7%)	26 (4.0%)
Non-compliance with study drug	14 (2.2%)	12 (1.8%)
Additional primary malignancy	11 (1.7%)	6 (0.9%)
Death	8 (1.2%)	5 (0.8%)
COVID-19 related death [c]	0	0
Lost to follow-up	4 (0.6%)	1 (0.2%)
Other	3 (0.5%)	4 (0.6%)
COVID-19 pandemic related other reason	0	1 (0.2%)
Physician decision	3 (0.5%)	6 (0.9%)
Protocol violation	1 (0.2%)	0
Ongoing with study treatment (as of the cut-off date)	299 (45.9%)	125 (19.1%)

Abbreviations: COVID-19=Coronavirus disease 2019; FAS=Full analysis set; GCP=Good clinical practice; N=Total number of patients; n=Number of patients within category; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: 1306 patients were randomized. One patient was excluded from analysis due to a GCP violation (Module 5.3.5.1, Report PH-42024, Sections 8.2.3 and 8.3).

b: The analysis sets in this table are presented based on the randomized treatment assignment. One patient was randomized to the placebo+docetaxel arm but received at least one dose of darolutamide. This patient was included in the darolutamide+docetaxel arm in the analysis of all safety variables.

c: Although there were in total 6 patients with fatal (Grade 5) TEAEs reported that were related to COVID-19 (Section 2.1.11), none of these were reported by the investigator as being the primary reason for discontinuation of the treatment period.

- *mCRPC pool*

Table 54 Pooled Phase1/2 studies in mCRPC patients

Study no	Phase	Population	FPFV	LPLV or latest cut-off	Report no	Study status	Dose (mg BID)	Treated patients in mCRPC pool (SAF)
17829	1/2	mCRPC	28 MAR 2011	09 JUL 2013	R-9584,	Completed	100	42
18035 [a]			30 JUN 2011	21 OCT 2015	R-11102		200	44
							300	3
							500	4
							700	38
							900	3
							Total	**134**
17830	1	mCRPC	14 MAR 2013	30 APR 2017	R-9789,	Completed	600	**30**
			14 MAR 2013	18 DEC 2020 [b]	Addendum R-13926			
17719	1	mCRPC	23 FEB 2015	09 MAY 2016	PH-39192,	Completed	300	3
			23 FEB 2015	21 DEC 2017 [c]	Addendum PH-40296		600	6
							Total	9
TOTAL number of patients in the pool						**Darolutamide**		**173**

Abbreviations: BID=Twice daily; FPFV=First patient first visit; LPLV=Last patient last visit; mCRPC=Metastatic castration-resistant prostate cancer; SAF=Safety analysis set

a: In the integrated safety analysis, the data from Study 18035 (long-term safety follow-up of 76 patients who continued treatment after the 12-week treatment period of Study 17829) are pooled with the safety data from Study 17829.

b: Only the data collected between 30 APR 2017 (cut-off for the main report) and 18 DEC 2020 (LPLV) for the 6 patients who continued on treatment after the report cut-off are included in the report addendum (Module 5.3.1.1, Report Addendum R-13926).

c: Only the data collected between 09 MAY 2016 (cut-off for the main report) and 21 DEC 2017 (LPLV) for the one patient who continued on treatment after the report cut-off are included in the report addendum (Module 5.3.3.2, Report Addendum PH-40296).

Table 55 Treatment duration in mCRPC pool (SAF)

	Total N=173
Duration of treatment (months) [a]	
Mean (StD)	10.49 (12.92)
Min, Max	0.0, 90.0
Median	6.50
Duration of treatment – categories (months), n (%)	
≤1	8 (4.6%)
>1 to ≤6	76 (43.9%)
>6 to ≤12	40 (23.1%)
>12 to ≤18	23 (13.3%)
>18 to ≤24	13 (7.5%)
>24 to ≤30	4 (2.3%)
>30 to ≤36	2 (1.2%)
>36	7 (4.0%)

Abbreviations: mCRPC=Metastatic castration-resistant prostate cancer; N=Total number of patients (100%); n=Number of patients within category; Max=Maximum; Min=Minimum; SAF=Safety analysis set, StD=Standard deviation

a: Months: (day of last dose minus day of first dose + 1) / 30.44.

- *Non-cancer patients*

The integrated analysis of safety in non-cancer subjects included single dose clinical studies in healthy volunteers and subjects with renal or hepatic impairment. All dose groups were pooled.

Table 56 Pooled Phase 1 single dose studies in non-cancer subjects

Study no	Population	FSFV	LSLV	Report no	Study status	Exposed subjects (SAF) Non-cancer subject pool
17721	Healthy Moderate HI Severe RI	13 SEP 2016	10 APR 2017	PH-39976	Completed	10 9 10
17726	Healthy	15 FEB 2017	04 MAY 2017	PH-40010	Completed	15
17831	Healthy	26 MAR 2015	20 MAY 2015	R-11003	Completed	12
18426	Healthy	23 OCT 2018	01 OCT 2019	PH-41300	Completed	24
TOTAL number of subjects in the pool						**80**

Abbreviations: FSFV=First subject first visit, HI=Hepatic impairment; LSLV=Last subject last visit; RI=Renal impairment; SAF=Safety analysis set

Adverse events

- *Study 17777 (ARASENS)*

An overview of TEAEs in mHSPC patients treated with darolutamide or placebo in combination with docetaxel in Study 17777 as of the database cut-off date for the primary completion analysis (25 OCT 2021) is presented in **Table *57***.

Table 57 Overview of TEAEs in Study 17777 (SAF)

Number of patients (%) with:	Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Any TEAE [a]	**649 (99.5%)**	**643 (98.9%)**
Worst Grade 1	28 (4.3%)	35 (5.4%)
Grade 2	162 (24.8%)	169 (26.0%)
Grade 3	248 (38.0%)	232 (35.7%)
Grade 4	183 (28.1%)	181 (27.8%)
Grade 5	27 (4.1%)	26 (4.0%)
Missing	1 (0.2%)	0
Grade 1 or 2	190 (29.1%)	204 (31.4%)
Grade 3 or 4	431 (66.1%)	413 (63.5%)
Grade 3, 4 or 5	458 (70.2%)	439 (67.5%)
TESAE	292 (44.8%)	275 (42.3%)
TEAE leading to study drug dose modification [b]	169 (25.9%)	112 (17.2%)
TEAE leading to permanent discontinuation of study drug [c]	88 (13.5%)	69 (10.6%)
TEAE leading to docetaxel dose modification [b]	214 (32.8%)	214 (32.9%)
TEAE leading to permanent discontinuation of docetaxel [c]	52 (8.0%)	67 (10.3%)
Related to protocol-required procedure	66 (10.1%)	63 (9.7%)

Number of patients (%) with:	Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Any study drug-related TEAE [a, d]	**340 (52.1%)**	**308 (47.4%)**
Worst Grade 1	140 (21.5%)	144 (22.2%)
Grade 2	138 (21.2%)	123 (18.9%)
Grade 3	53 (8.1%)	31 (4.8%)
Grade 4	9 (1.4%)	7 (1.1%)
Grade 5	0	3 (0.5%)
Grade 1 or 2	278 (42.6%)	267 (41.1%)
Grade 3 or 4	62 (9.5%)	38 (5.8%)
Grade 3, 4 or 5	62 (9.5%)	41 (6.3%)
Study drug-related TESAE	29 (4.4%)	23 (3.5%)
Study drug-related TEAE leading to study drug dose modification [b]	75 (11.5%)	41 (6.3%)
Study drug-related TEAE leading to permanent discontinuation of study drug [c]	25 (3.8%)	13 (2.0%)
Any docetaxel-related TEAE [a, d]	**573 (87.9%)**	**575 (88.5%)**
Worst Grade 1	111 (17.0%)	115 (17.7%)
Grade 2	183 (28.1%)	183 (28.2%)
Grade 3	117 (17.9%)	112 (17.2%)
Grade 4	160 (24.5%)	161 (24.8%)
Grade 5	1 (0.2%)	4 (0.6%)
Missing	1 (0.2%)	0
Grade 1 or 2	294 (45.1%)	298 (45.8%)
Grade 3 or 4	277 (42.5%)	273 (42.0%)
Grade 3, 4 or 5	278 (42.6%)	277 (42.6%)
Docetaxel-related TESAE	110 (16.9%)	105 (16.2%)
Docetaxel-related TEAE leading to docetaxel dose modification [b]	179 (27.5%)	180 (27.7%)
Docetaxel-related TEAE leading to permanent discontinuation of docetaxel [c]	45 (6.9%)	57 (8.8%)

Abbreviations: AE=Adverse event; CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of patients (100%); n=Number of patients with event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event; TESAE=Treatment-emergent serious adverse event

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

b: Modifications include dose interruptions/delays and reductions.

c: Discontinuation of study drug (darolutamide/placebo) and docetaxel due to an AE was calculated for AEs where action taken was checked as "Drug Withdrawn".

d: Based on investigator's assessment.

CTCAE version 4.03.

Most common TEAEs

An overview of the TEAEs reported in ≥10% of patients in either treatment arm of Study 17777 is presented in **Table *58*** by MedDRA Preferred Term (PT). To adjust for potential differences in study drug treatment duration between the treatment arms, exposure-adjusted incidence rates (EAIRs) per 100 PYs are also summarized.

Table 58 Incidences and exposure-adjusted incidence rates of the most common TEAEs by MedDRA PT occurring in ≥10% of patients in either treatment arm in Study 17777 (SAF)

	Darolutamide+ docetaxel arm N=652					Placebo+ docetaxel arm N=650				
MedDRA PT v. 24.1	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 (%)
Alopecia	264 (40.5)	15.3	1 (0.2)	0	0	264 (40.6)	22.0	2 (0.3)	0	0
Fatigue	216 (33.1)	12.5	11 (1.7)	0	0	214 (32.9)	17.8	12 (1.8)	0	0
Anaemia	181 (27.8)	10.5	29 (4.4)	2 (0.3)	0	163 (25.1)	13.6	32 (4.9)	1 (0.2)	0
Arthralgia	178 (27.3)	10.3	8 (1.2)	0	0	174 (26.8)	14.5	9 (1.4)	0	0
Oedema peripheral	173 (26.5)	10.0	2 (0.3)	1 (0.2)	0	169 (26.0)	14.1	1 (0.2)	0	0
Neutrophil count decreased	170 (26.1)	9.8	39 (6.0)	12 (17.2)	0	155 (23.8)	12.9	41 (6.3)	99 (15.2)	0
Diarrhoea	167 (25.6)	9.6	8 (1.2)	0	0	156 (24.0)	13.0	7 (1.1)	0	0
White blood cell count decreased	155 (23.8)	9.0	86 (13.2)	24 (3.7)	0	143 (22.0)	11.9	80 (12.3)	17 (2.6)	0
Constipation	147 (22.5)	8.5	2 (0.3)	0	0	130 (20.0)	10.8	2 (0.3)	0	0
Hot flush	124 (19.0)	7.2	0	0	0	122 (18.8)	10.2	1 (0.2)	0	0
Back pain	123 (18.9)	7.1	12 (1.8)	0	0	123 (18.9)	10.2	11 (1.7)	0	0
Decreased appetite	121 (18.6)	7.0	1 (0.2)	0	0	85 (13.1)	7.1	4 (0.6)	0	0
Weight increased	116 (17.8)	6.7	14 (2.1)	0	0	102 (15.7)	8.5	8 (1.2)	0	0
Nausea	115 (17.6)	6.6	3 (0.5)	0	0	133 (20.5)	11.1	2 (0.3)	0	0
Alanine aminotransferase increased	102 (15.6)	5.9	17 (2.6)	1 (0.2)	0	84 (12.9)	7.0	9 (1.4)	2 (0.3)	0
Pain in extremity	98 (15.0)	5.7	2 (0.3)	0	0	78 (12.0)	6.5	2 (0.3)	0	0
Aspartate aminotransferase increased	91 (14.0)	5.3	16 (2.5)	1 (0.2)	0	68 (10.5)	5.7	6 (0.9)	1 (0.2)	0
Pyrexia	86 (13.2)	5.0	3 (0.5)	0	0	90 (13.8)	7.5	3 (0.5)	0	0
Hypertension	85 (13.0)	4.9	42 (6.4)	0	1 (0.2)	59 (9.1)	4.9	21 (3.2)	0	0
Cough	84 (12.9)	4.9	0	0	0	73 (11.2)	6.1	0	0	0
Bone pain	81 (12.4)	4.7	8 (1.2)	0	0	84 (12.9)	7.0	17 (2.6)	2 (0.3)	0
Neuropathy peripheral	76 (11.7)	4.4	3 (0.5)	0	0	67 (10.3)	5.6	0	0	0
Hyperglycaemia	74 (11.3)	4.3	17 (2.6)	1 (0.2)	0	61 (9.4)	5.1	20 (3.1)	4 (0.6)	0
Insomnia	74 (11.3)	4.3	0	0	0	81 (12.5)	6.7	0	0	0
Myalgia	73 (11.2)	4.2	2 (0.3)	0	0	63 (9.7)	5.2	2 (0.3)	0	0
Dysgeusia	69 (10.6)	4.0	0	0	0	80 (12.3)	6.7	0	0	0
Asthenia	68 (10.4)	3.9	1 (0.2)	0	0	65 (10.0)	5.4	3 (0.5)	0	0
Neutropenia	68 (10.4)	3.9	18 (2.8)	38 (5.8)	0	76 (11.7)	6.3	18 (2.8)	50 (7.7)	0
Stomatitis	66 (10.1)	3.8	4 (0.6)	0	0	57 (8.8)	4.7	4 (0.6)	0	0
Peripheral sensory neuropathy	65 (10.0)	3.8	2 (0.3)	0	0	67 (10.3)	5.6	2 (0.3)	0	0
Urinary tract infection	61 (9.4)	3.5	13 (2.0)	0	0	67 (10.3)	5.6	12 (1.8)	0	0
Dyspnoea	59 (9.0)	3.4	2 (0.3)	0	0	71 (10.9)	5.9	4 (0.6)	0	1 (0.2)
Malaise	57 (8.7)	3.3	0	0	0	66 (10.2)	5.5	0	0	0

Abbreviations: 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; PT=Preferred term, PY=Patient year; 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 study drug treatment duration of all patients in years. The rate is expressed in number of patients with events per 100 PYs.
The EAIR is less relevant for adverse events that are known to occur with docetaxel and occurred predominantly during the first 6 months of study treatment (Section 2.1.2.2).

Note:
A patient may have more than one entry.
The total column also includes patients with a missing CTCAE grade (2 patients with white blood cell count decreased and 1 patient with edema peripheral in the darolutamide+docetaxel arm, and 1 patient with hypertension in the placebo+docetaxel

TEAEs over time

The incidence (new or worsening TEAEs) and prevalence of the most commonly reported TEAEs were analyzed within pre-specified time intervals (3-month intervals for the first year and 6-month intervals from thereafter up to 24 months) in Study 17777.

Incidences of commonly reported TEAEs, including alopecia, fatigue, anaemia, arthralgia, oedema peripheral, neutrophil count decreased, diarrhoea, WBC count decreased, neuropathy peripheral, and peripheral sensory neuropathy, were highest during the first 3 months of treatment and started to decrease during Months 4 to 6 after the start of study treatment in both treatment arms. A further

decrease was seen during Months 7 to 12, after completing the docetaxel treatment (data not shown) The incidences of these events then remained stable during continued treatment with study drug.

Prevalence followed a similar general trend for most of the TEAEs listed above; however, the prevalence of TEAEs decreased over a longer period of time. The prevalence of neuropathy peripheral and peripheral sensory neuropathy remained stable throughout the whole study in both treatment arms. A trend of increasing prevalence of arthralgia, hypertension, and hyperglycaemia was observed in both treatment arms.

Analysis of AEs by system organ class (***SOC)***

A summary of TEAEs by MedDRA SOC and worst CTCAE grade in Study 17777 is shown below.

Table 59 Incidence of TEAEs by MedDRA SOC and worst grade in Study 17777 (SAF)

	Darolutamide+ docetaxel arm N=652 n (%)						Placebo+ docetaxel arm N=650 n (%)					
MedDRA SOC v. 24.1	Worst CTCAE grade						Worst CTCAE grade					
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
All SOCs	**648 (99.4)**	**28 (4.3)**	**162 (24.8)**	**248 (38.0)**	**183 (28.1)**	**27 (4.1)**	**643 (98.9)**	**35 (5.4)**	**169 (26.0)**	**232 (35.7)**	**181 (27.8)**	**26 (4.0)**
General disorders and administration site conditions	461 (70.7)	250 (38.3)	181 (27.8)	25 (3.8)	1 (0.2)	4 (0.6)	458 (70.5)	239 (36.8)	188 (28.9)	21 (3.2)	1 (0.2)	9 (1.4)
Musculoskeletal and connective tissue disorders	421 (64.6)	191 (29.3)	179 (27.5)	51 (7.8)	0	0	406 (62.5)	191 (29.4)	160 (24.6)	52 (8.0)	3 (0.5)	0
Skin and subcutaneous tissue disorders	418 (64.1)	245 (37.6)	153 (23.5)	19 (2.9)	1 (0.2)	0	398 (61.2)	245 (37.7)	149 (22.9)	4 (0.6)	0	0
Gastrointestinal disorders	405 (62.1)	216 (33.1)	155 (23.8)	33 (5.1)	1 (0.2)	0	411 (63.2)	221 (34.0)	156 (24.0)	30 (4.6)	3 (0.5)	1 (0.2)
Investigations	375 (57.5)	87 (13.3)	79 (12.1)	89 (13.7)	120 (18.4)	0	353 (54.3)	74 (11.4)	72 (11.1)	96 (14.8)	111 (17.1)	0
Nervous system disorders	344 (52.8)	206 (31.6)	96 (14.7)	36 (5.5)	3 (0.5)	3 (0.5)	342 (52.6)	214 (32.9)	95 (14.6)	31 (4.8)	1 (0.2)	1 (0.2)
Infections and infestations	320 (49.1)	71 (10.9)	155 (23.8)	73 (11.2)	15 (2.3)	6 (0.9)	309 (47.5)	66 (10.2)	165 (25.4)	62 (9.5)	10 (1.5)	6 (0.9)
Metabolism and nutrition disorders	273 (41.9)	134 (20.6)	83 (12.7)	48 (7.4)	8 (1.2)	0	222 (34.2)	76 (11.7)	78 (12.0)	56 (8.6)	11 (1.7)	1 (0.2)
Blood and lymphatic system disorders	270 (41.4)	60 (9.2)	69 (10.6)	94 (14.4)	47 (7.2)	0	266 (40.9)	64 (9.8)	58 (8.9)	83 (12.8)	61 (9.4)	0
Vascular disorders	243 (37.3)	100 (15.3)	91 (14.0)	50 (7.7)	1 (0.2)	1 (0.2)	233 (35.8)	116 (17.8)	89 (13.7)	26 (4.0)	2 (0.3)	0
Respiratory, thoracic and mediastinal disorders	227 (34.8)	131 (20.1)	72 (11.0)	17 (2.6)	3 (0.5)	4 (0.6)	229 (35.2)	128 (19.7)	70 (10.8)	22 (3.4)	5 (0.8)	4 (0.6)
Renal and urinary disorders	189 (29.0)	100 (15.3)	56 (8.6)	30 (4.6)	3 (0.5)	0	177 (27.2)	91 (14.0)	53 (8.2)	30 (4.6)	1 (0.2)	2 (0.3)
Injury, poisoning and procedural complications	129 (19.8)	53 (8.1)	58 (8.9)	17 (2.6)	0	1 (0.2)	102 (15.7)	43 (6.6)	39 (6.0)	19 (2.9)	1 (0.2)	0
Psychiatric disorders	114 (17.5)	74 (11.3)	37 (5.7)	2 (0.3)	1 (0.2)	0	126 (19.4)	85 (13.1)	41 (6.3)	0	0	0
Eye disorders	100 (15.3)	62 (9.5)	26 (4.0)	12 (1.8)	0	0	96 (14.8)	64 (9.8)	24 (3.7)	8 (1.2)	0	0
Cardiac disorders	83 (12.7)	35 (5.4)	27 (4.1)	12 (1.8)	4 (0.6)	5 (0.8)	90 (13.8)	39 (6.0)	31 (4.8)	16 (2.5)	1 (0.2)	3 (0.5)
Reproductive system and breast disorders	67 (10.3)	39 (6.0)	27 (4.1)	1 (0.2)	0	0	57 (8.8)	21 (3.2)	28 (4.3)	8 (1.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	50 (7.7)	12 (1.8)	11 (1.7)	21 (3.2)	2 (0.3)	4 (0.6)	39 (6.0)	17 (2.6)	11 (1.7)	10 (1.5)	1 (0.2)	0
Ear and labyrinth disorders	30 (4.6)	22 (3.4)	5 (0.8)	2 (0.3)	1 (0.2)	0	29 (4.5)	21 (3.2)	6 (0.9)	2 (0.3)	0	0
Hepatobiliary disorders	28 (4.3)	15 (2.3)	6 (0.9)	4 (0.6)	3 (0.5)	0	31 (4.8)	12 (1.8)	13 (2.0)	5 (0.8)	0	1 (0.2)
Immune system disorders	27 (4.1)	9 (1.4)	15 (2.3)	2 (0.3)	1 (0.2)	0	9 (1.4)	4 (0.6)	3 (0.5)	2 (0.3)	0	0
Surgical and medical procedures	13 (2.0)	4 (0.6)	0	9 (1.4)	0	0	6 (0.9)	2 (0.3)	2 (0.3)	2 (0.3)	0	0
Endocrine disorders	9 (1.4)	3 (0.5)	6 (0.9)	0	0	0	9 (1.4)	6 (0.9)	3 (0.5)	0	0	0
Congenital, familial and genetic disorders	3 (0.5)	0	2 (0.3)	1 (0.2)	0	0	2 (0.3)	1 (0.2)	1 (0.2)	0	0	0
Product issues	2 (0.3)	0	2 (0.3)	0	0	0	4 (0.6)	0	2 (0.3)	2 (0.3)	0	0
Social circumstances	1 (0.2)	0	1 (0.2)	0	0	0	0	0	0	0	0	0

Abbreviations: 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; SAF=Safety analysis set; SOC=System organ class; TEAE=Treatment-emergent adverse event

Note: Any adverse events with missing CTCAE grade are not included in this summary table.

CTCAE version 4.03.

Grade ≥3 TEAEs

TEAEs of Grade 3 or 4 as the worst grade occurring in ≥1.5% of patients in either treatment arm in Study 17777 are presented by MedDRA PT in the table below.

Table 60 Incidence of worst Grade 3 or 4 TEAEs by MedDRA PT occurring in ≥1.5% of patients in either treatment arm in Study 17777 (SAF)

MedDRA PT v. 24.1	Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Neutrophil count decreased	151 (23.2%)	140 (21.5%)
White blood cell count decreased	110 (16.9%)	97 (14.9%)
Neutropenia	56 (8.6%)	68 (10.5%)
Febrile neutropenia	51 (7.8%)	48 (7.4%)
Hypertension	42 (6.4%)	21 (3.2%)
Anaemia	31 (4.8%)	33 (5.1%)
Pneumonia	21 (3.2%)	20 (3.1%)
Hyperglycaemia	18 (2.8%)	24 (3.7%)
Alanine aminotransferase increased	18 (2.8%)	11 (1.7%)
Aspartate aminotransferase increased	17 (2.6%)	7 (1.1%)
Leukopenia	15 (2.3%)	19 (2.9%)
Weight increased	14 (2.1%)	8 (1.2%)
Urinary tract infection	13 (2.0%)	12 (1.8%)
Back pain	12 (1.8%)	11 (1.7%)
Syncope	12 (1.8%)	11 (1.7%)
Hyponatraemia	12 (1.8%)	9 (1.4%)
Fatigue	11 (1.7%)	12 (1.8%)
Blood alkaline phosphatase increased	10 (1.5%)	12 (1.8%)
Bone pain	8 (1.2%)	19 (2.9%)

Abbreviations: 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; PT=Preferred term, SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Note:
A patient may have more than one entry.
Any adverse events with missing CTCAE grade are not included in this summary table.

TEAEs of special -topic

Special topics were defined as events/disorders representing potential or known risks associated with ADT or with anti-androgens.

The overall incidences and EAIRs of the TEAEs of special topics in Study 17777 are presented in the table below.

Table 61 Incidences and exposure-adjusted incidence rates of TEAEs of special interest associated with ADT or anti-androgens in Study 17777 (SAF)

Grouped TEAE term [a]	Darolutamide+ docetaxel arm N=652 n (%)	Darolutamide+ docetaxel arm EAIR per 100 PY [b]	Placebo+ docetaxel arm N=650 n (%)	Placebo+ docetaxel arm EAIR per 100 PY [b]	Incidence risk ratio for EAIR
Fatigue/asthenic conditions	315 (48.3%)	18.2	319 (49.1%)	26.5	0.69
Bone fractures (excluding pathological fractures)	49 (7.5%)	2.8	33 (5.1%)	2.7	1.03
Fall	43 (6.6%)	2.5	30 (4.6%)	2.5	1.00
Vasodilatation and flushing	133 (20.4%)	7.7	141 (21.7%)	11.7	0.66
Breast disorders/gynecomastia	21 (3.2%)	1.2	10 (1.5%)	0.8	1.46
Rash	108 (16.6%)	6.2	88 (13.5%)	7.3	0.85
Hypertension [c]	90 (13.8%)	5.2	61 (9.4%)	5.1	1.02
Cardiac disorders	71 (10.9%)	4.1	76 (11.7%)	6.3	0.65
Cardiac arrhythmias	52 (8.0%)	3.0	55 (8.5%)	4.6	0.66
Coronary artery disorders	19 (2.9%)	1.1	13 (2.0%)	1.1	1.01
Heart failures	4 (0.6%)	0.2	13 (2.0%)	1.1	0.21
Diabetes mellitus and hyperglycemia	99 (15.2%)	5.7	93 (14.3%)	7.7	0.74
Mental impairment disorders	23 (3.5%)	1.3	15 (2.3%)	1.2	1.06
Depressed mood disorders	21 (3.2%)	1.2	24 (3.7%)	2.0	0.61
Cerebral ischaemia	8 (1.2%)	0.5	8 (1.2%)	0.7	0.69
Cerebral and intracranial hemorrhage	6 (0.9%)	0.3	1 (0.2%)	0.1	4.17
Seizure	4 (0.6%)	0.2	1 (0.2%)	0.1	2.78
Weight decreased	22 (3.4%)	1.3	35 (5.4%)	2.9	0.44

Abbreviations: ADT=Androgen deprivation therapy; EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of patients (100%); n=Number of patients with event; PT=Preferred term; PY=Patient year; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: The specific terms used for MedDRA searches and reported PTs for pre-defined grouped TEAE terms are described in SAP v. 4.1, Module 5.3.5.1, Report PH-42024, Table 9-2 of Section 16.1.9 and Table 14.3.1/44, respectively.

b: EAIR of grouped events, defined as the number of patients with a given TEAE divided by the total study drug treatment duration of all patients in years. The rate is expressed in number of patients with events per 100 PYs.

c: The MedDRA search terms and reported PTs for data-driven grouping hypertension are provided in Module 5.3.5.1, Report PH-42024, Table 14.3.1.2/12s1 (post-hoc).

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

- *Hypertension*

Approximately half of the patients in both the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (51.3% vs. 49.2%, respectively) had a medical history of hypertension (single PT) in the FAS.

Medical history of blood pressure increased was reported for 0.5% vs. 0.2% of patients, and essential hypertension for 1.4% of patients in both the darolutamide + docetaxel + ADT and placebo + docetaxel + ADT arms, respectively.

Pre-treatment AEs of hypertension (single PT) were reported with a slightly higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (2.5% vs 1.7%, respectively).

Treatment-emergent events of hypertension (data-driven grouping) were more commonly reported in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm 13.8% vs. 9.4%, respectively). When adjusted for the difference in study drug treatment duration, the EAIRs of hypertension were similar between the arms (5.2 vs. 5.1 per 100 PY), with an incidence risk ratio of 1.02. The events within this group were mainly driven by a single PT hypertension (13.0% vs 9.1%).

Although the incidence of Grade 1 and 2 hypertension events (data-driven grouping) were similar between the treatment arms, hypertension events with Grade 3 as the worst grade were more commonly reported in the darolutamide + docetaxel + ADT arm (6.4%) than in the placebo + docetaxel + ADT arm (3.5%). There was 1 patient with a Grade 4 event of hypertension in both the darolutamide + docetaxel + ADT arm (hypertensive emergency) and the placebo + docetaxel + ADT arm (hypertensive crisis).

One patient in the darolutamide + docetaxel + ADT treatment arm was reported with two Grade 5 events (hypertension and arteriosclerosis). As per the patient's death certificate, the patient died due to hypertensive and atherosclerotic cardiovascular disease. The investigator and sponsor did not suspect a causal relationship to darolutamide. There were no Grade 5 events in the placebo + docetaxel + ADT arm.

Overall, TEAEs of hypertension were reported more commonly in patients with no medical history of hypertension in both treatment arms, and the incidences were higher in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (16.4% vs. 10.3% of patients, respectively). Among the patients with medical history of hypertension, the incidence of TEAEs of hypertension with worst grade of 3 was higher in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (7.2% vs. 3.9%, respectively). The incidence of hypertension with worst grade of 3 was also higher in patients without history of hypertension in the darolutamide +docetaxel arm compared with the placebo+docetaxel + ADT arm (5.6% vs 3.1%).

Table 62 Incidence of TEAEs hypertension by present history of hypertension (MLG) and worst CTCAE grade in Study 17777 (SAF)

		Darolutamide+ docetaxel arm		Placebo+ docetaxel arm	
MLG MedDRA v. 24.1	Worst CTCAE grade	History of hypertension N=347 n (%)	No history of hypertension N=305 n (%)	History of hypertension N=330 n (%)	No history of hypertension N=320 n (%)
Hypertension [a]	**Total**	**39 (11.2%)**	**50 (16.4%)**	**27 (8.2%)**	**33 (10.3%)**
	Grade 1	3 (0.9%)	12 (3.9%)	2 (0.6%)	6 (1.9%)
	Grade 2	10 (2.9%)	21 (6.9%)	11 (3.3%)	17 (5.3%)
	Grade 3	25 (7.2%)	17 (5.6%)	13 (3.9%)	10 (3.1%)
	Grade 5	1 (0.3%)	0	0	0
	Missing	0	0	1 (0.3%)	0

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; MLG=MedDRA labeling grouping; N=Total number of patients (100%); n=Number of patients with event; PT=Preferred term; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event;
a: The MLG hypertension includes reported PTs hypertension and blood pressure increased. No Grade 4 events were reported within the MLG hypertension.
CTCAE version 4.03

- *Rash*

Treatment-emergent events of rash were reported with a higher incidence in the darolutamide + docetaxel + ADT arm compared with the placebo + docetaxel + ADT arm (16.6% vs. 13.5%, respectively). When adjusted for the difference in study drug treatment duration, the EAIRs of rash were similar between the arms (6.2 vs. 7.3 per 100 PY), with an incidence risk ratio of 0.85. At the PT level, the most commonly reported TEAE within this group was an unspecific term rash in both treatment arms (7.8% vs. 6.9%).

Events of rash were reported with a worst grade of 1 or 2 in severity in most patients. Events with a worst grade of 3 were reported with a slightly higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (1.2% vs. 0.2%), respectively. At the PT level, the difference was mainly driven by Grade 3 rash maculo-papular (0.6% vs. 0%), followed by Grade 3 drug eruption (0.3% vs. 0%) and Grade 3 rash (0.3% vs. 0.2%). Grade 4 rash (PT drug eruption) was reported in 1 patient (0.2%) in the darolutamide + docetaxel + ADT arm whereas no Grade 4 events of rash were observed in the placebo + docetaxel + ADT arm.

The events of rash were considered serious in 1 patient (0.2%) in both treatment arms. Study drug and docetaxel were permanently discontinued due to rash in 1.1% and 0.9% of patients in the darolutamide + docetaxel + ADT arm, respectively, with no permanent discontinuations being reported in the placebo + docetaxel + ADT arm. Study drug dose was interrupted in 1.4% vs. 0.2% of patients and reduced in 0.5% vs. 0% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. Docetaxel dose was interrupted in 0.6% vs. 0.5% of patients and reduced in 1.1% vs. 0.5% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively.

- *Cardiac disorders*

The overall incidence (12.7% vs. 13.8%) of TEAEs within the SOC cardiac disorders was similar in the darolutamide + docetaxel + ADT arm and in the placebo + docetaxel + ADT arm, respectively. The events were mostly reported with Grade 1 or 2 as the worst grade in both treatment arms. Grade 5 events within the SOC cardiac disorders included 5 patients (0.8%) in the darolutamide + docetaxel + ADT arm and 3 patients (0.5%) in the placebo + docetaxel + ADT arm. The events were mostly reported with Grade 1 or 2 as the worst grade in both treatment arms. Grade 5 events within the SOC cardiac disorders included 5 patients (0.8%) in the darolutamide + docetaxel + ADT arm and 3 patients (0.5%) in the placebo + docetaxel + ADT arm.

Altogether, 112 patients in the darolutamide + docetaxel + ADT arm and 128 patients in the placebo + docetaxel + ADT arm had a medical history of cardiac disorders before the start of study treatment. In both treatment arms, the incidence of TEAEs within the SOC cardiac disorders was higher in patients who had a history of cardiac disorders, and this difference was more evident in patients in the placebo + docetaxel + ADT arm:

- Darolutamide + docetaxel + ADT arm

o History of cardiac disorders: 20/112 patients (17.9%)

o No history of cardiac disorders: 63/540 patients (11.7%)

- Placebo + docetaxel + ADT arm

o History of cardiac disorders: 37/128 patients (28.9%)

o No history of cardiac disorders: 53/522 patients (10.2%)

TEAEs within the HLGT (High Level Group Term) cardiac arrhythmias were reported with a similar incidence (8.0% vs. 8.5%) in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. The most common PTs within this HLGT were sinus tachycardia (1.5% in both arms), tachycardia (1.4% vs. 1.5%), atrial fibrillation (1.4% vs. 1.2%) and sinus bradycardia (1.1% and 0.6%) in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively.

TEAEs within the HLGT coronary artery disorders were reported with a small difference between the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (2.9% vs. 2.0%, respectively). When adjusted for the difference in study drug treatment duration, the EAIR was 1.1 per 100 PY in both treatment arms. The most common PTs within this HLGT were myocardial infarction (0.9% vs. 0.3%), acute myocardial infarction (0.5% vs. 0.5%), and angina pectoris (0.5% vs. 0.3%) in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. Two fatal events of myocardial infarction were reported in the darolutamide + docetaxel + ADT arm.

TEAEs within the HLGT heart failures were reported in 0.6% vs. 2.0% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. Of note, the most commonly reported TEAEs within this HLGT were less frequent in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm, respectively: cardiac failure (0.2% vs. 1.4%) and left ventricular failure (0% vs. 0.6%).

- *Diabetes mellitus and hyperglycaemia*

TEAEs of diabetes mellitus and hyperglycaemia were reported with a similar incidence between the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (15.2% vs. 14.3%, respectively). At the PT level, the most commonly reported TEAE within this group was hyperglycaemia in both treatment arms (11.3% vs. 9.4%). Events of diabetes mellitus and hyperglycaemia were reported with a worst grade of 3 in 3.5% vs. 4.5% of patients, and with a worst grade of 4 in 0.2% vs. 0.9% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. An analysis of diabetes mellitus and hyperglycaemia over time showed that both the incidence and prevalence of Grade 3 or 4 events were highest during the first 3 months of treatment and decreased thereafter in both treatment arms, whereas there was a consistent increase in the prevalence of Grade 1 or 2 events over time in both treatment arms.

The events of diabetes mellitus were considered serious in 0.5% vs. 1.1% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. No study

drug or docetaxel discontinuations, dose interruptions or dose reductions were reported in the darolutamide + docetaxel + ADT arm.

- *Fatigue/asthenic conditions*

TEAEs of special topics were most commonly reported within the grouped term of fatigue/asthenic conditions in both the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (48.3% vs. 49.1%, respectively). At the PT level, the most commonly reported TEAE within this group was fatigue, which was also reported with a similar incidence in both treatment arms (33.1% vs. 32.9%). An analysis of fatigue/asthenic conditions events over time showed that the events were predominantly reported during the first months from the start of study treatment in both treatment arms. The events of fatigue/asthenic conditions were considered serious in 0.5% vs. 0.3% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. The events resulted in study drug dose interruption in 0.8% vs. 0.2% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively, and in dose reduction in 0.6% of patients in both treatment arms.

- *Bone fractures (excluding pathological fractures)*

TEAEs of bone fracture were reported with a small difference between the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (7.5% vs. 5.1%, respectively). When adjusted for the difference in study drug treatment duration, the EAIRs of bone fractures were similar between the treatment arms (2.8 vs. 2.7 per 100 PY), with an incidence risk ratio of 1.03. Of note, there were 1.1% of patients in the darolutamide + docetaxel + ADT arm and 0.5% of patients in the placebo + docetaxel + ADT arm who had pathological fracture (not part of the grouped term).

Bone fractures were reported with a worst grade of 1 or 2 in severity in most patients. Events with a worst grade of 3 were reported in 1.5% of patients in the darolutamide + docetaxel + ADT arm and in 2.3% in the placebo + docetaxel + ADT arm. The bone fracture events were considered serious in 1.4% vs. 1.5% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. Study drug was permanently discontinued due to bone fracture in 0.3% of patients in the placebo + docetaxel + ADT arm with no respective events reported in the darolutamide + docetaxel + ADT arm.

- *Fall*

Treatment-emergent events of fall were reported with a small difference between the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (6.6% vs. 4.6%, respectively). When adjusted for the difference in study drug treatment duration, the EAIRs of fall were 2.5 per 100 PY in both treatment arms, with an incidence risk ratio of 1.00. Almost all events within this group were due to a PT fall. The events of fall were reported with a worst grade of 1 or 2 in severity in most patients and thus were minor with no resultant injuries or were symptomatic with noninvasive intervention needed. The fall events were considered serious in 0.3% of patients in the darolutamide + docetaxel + ADT arm and no serious events were reported in the placebo + docetaxel + ADT arm.

- *Vasodilatation and flushing*

Treatment-emergent events of vasodilatation and flushing were reported with a similar incidence in the darolutamide + docetaxel + ADT arm and in the placebo + docetaxel + ADT arm (20.4% vs. 21.7%, respectively).

- *Breast disorders/gynaecomastia*

TEAEs of breast disorders/gynaecomastia were more commonly reported in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (3.2% vs. 1.5%, respectively). When

adjusted for the difference in study drug treatment duration, the EAIRs of breast disorders/gynaecomastia were 1.2 vs. 0.8 per 100 PY, with an incidence risk ratio of 1.46.

All events of breast disorders/gynaecomastia were either Grade 1 or 2 as the worst grade in both treatment arms. No TESAEs, study drug or docetaxel discontinuations, dose interruptions or dose reductions were reported due to breast disorders/gynaecomastia in the darolutamide + docetaxel + ADT arm.

- *Mental impairment disorders*

TEAEs of mental impairment disorders were reported with a small difference between the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm (3.5% vs. 2.3%, respectively). When adjusted for the difference in study drug treatment duration, the EAIRs of mental impairment disorders were similar between the arms (1.3 vs. 1.2 per 100 PY), with an incidence risk ratio of 1.06. Grade 1 or 2 was the worst grade for all reported events. At the PT level, the most commonly reported TEAE within this group was memory impairment (1.2% vs. 0.9%), followed by cognitive disorder (0.9% vs. 0.5%) and disturbance in attention (0.8% vs. 0.5%) in both the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively.

- *Depressed mood disorders*

TEAEs of depressed mood disorders were reported with a similar incidence in the darolutamide + docetaxel + ADT arm and in the placebo + docetaxel + ADT arm (3.2% vs. 3.7%, respectively).

- *Cerebrovascular disorders*

TEAEs of cerebral ischemia were reported in 1.2% of patients in both treatment arms. Cerebral and intracranial hemorrhage were reported in 6 patients (0.9%) in the darolutamide + docetaxel + ADT arm and in 1 patient (0.2%) in the placebo + docetaxel + ADT arm. Confounding factors, such as preceding surgery, fall or underlying comorbidities (hypertension, aneurysma, thrombocytopenia), were identified for all 6 patients who had cerebral or intracranial hemorrhage in the darolutamide + docetaxel + ADT arm. None of the events were considered drug-related by the investigator.

- *Seizure*

During the study, seizure was reported in 4 patients (0.6%) in the darolutamide + docetaxel + ADT arm and in 1 patient (0.2%) in the placebo + docetaxel + ADT arm (Table 2–17). At the PT level, the events were seizure (3 patients) and focal dyscognitive seizures (1 patient) in the darolutamide + docetaxel + ADT arm, and epilepsy (1 patient) in the placebo + docetaxel + ADT arm.

All seizure events were of Grade 1 (0.2% vs. 0%) or Grade 2 (0.5% vs. 0.2%) in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. No study drug permanent discontinuations were reported due to seizure.

The 4 patients with a reported seizure in the darolutamide + docetaxel + ADT arm had no medical history of seizure. Two of these patients had confounding factors: CVA and movement disorders as medical history in one patient, and CVA as a co-reported event in another patient.

The third patient in the darolutamide + docetaxel + ADT arm had a history of anxiety and experienced focal dyscognitive seizures (reported term: complex partial epileptic crisis) 341 days after starting darolutamide treatment. Darolutamide dose was not changed as a result of this event.

The event was treated with valproic acid and levetiracetam. The fourth patient had a seizure between docetaxel cycles 1 and 2. The brain CT and electroencephalogram were without findings. Darolutamide dose was not changed, whereas docetaxel treatment was interrupted due to the event.

Overall, 2 of the 4 seizure events in the darolutamide + docetaxel + ADT arm occurred during the docetaxel treatment. The seizure event led to docetaxel interruption in 1 of the patients but darolutamide dose was not changed in either of these 2 patients.

- *Weight decreased*

TEAEs of weight decreased (single PT) were reported with a slightly lower incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (3.4% vs. 5.4%, respectively).

TEAEs commonly associated with docetaxel

The most common TEAEs in Study 17777 largely overlapped with the TEAEs commonly associated with docetaxel (alopecia, anaemia, neutrophil count decreased and neutropenia, diarrhoea, constipation, nausea, neuropathy peripheral and peripheral sensory neuropathy, myalgia, dysgeusia, asthenia, and dyspnoea).

- Neutrophil count decreased was one of the most commonly reported TEAEs occurring in 26.1% of patients in the darolutamide + docetaxel + ADT arm and in 23.8% of patients in the placebo + docetaxel + ADT arm. Neutropenia was reported in 10.4% and 11.7% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. Most of the patients with neutrophil count decreased or neutropenia had an event with a worst grade of 3 or 4 in both treatment arms (these were the most common Grade 4 TEAEs). Neutrophil count decreased was assessed as study drug-related by the investigator in 1.4% vs. 0.6% of patients, and docetaxel-related in 24.8% vs. 22.8% of patients in the darolutamide + docetaxel + ADT and the placebo + docetaxel + ADT arm, respectively. Neutropenia was assessed as study drug-related in 0.6% vs. 0.3% of patients, and docetaxel-related in 9.2% vs. 10.6% of patients in the darolutamide + docetaxel + ADT and the placebo + docetaxel + ADT arm.
- AST and ALT increased were reported as TEAEs with slightly higher incidences in the darolutamide + docetaxel + ADT arm (14.0% and 15.6% of patients, respectively) than in the placebo + docetaxel + ADT arm (10.5% and 12.9% of patients, respectively). AST increased and ALT increased were among the most commonly reported study drug-related TEAEs, TEAEs leading to permanent discontinuation of study drug or docetaxel, and TEAEs leading to study drug or docetaxel dose modifications.

Additional primary malignancies

In Study 17777, additional primary malignancies were reported in 25 patients (3.8%) in the darolutamide + docetaxel + ADT arm and in 16 patients (2.5%) in the placebo + docetaxel + ADT arm.

Additional primary malignancies reported in ≥2 patients in either the darolutamide + docetaxel + ADT arm or the placebo + docetaxel + ADT arm, respectively, are summarized below.

- Basal cell carcinoma: 3 patients (0.5%) vs. 1 patient (0.2%)
- Squamous cell carcinoma of skin: 2 patients (0.3%) vs. 2 patients (0.3%)
- Pancreatic carcinoma: 2 patients (0.3%) vs. 0 patients (0%)
- Squamous cell carcinoma: 2 patients (0.3%) vs. 0 patients (0%)

There was 1 patient in the darolutamide + docetaxel + ADT arm reported with a suspicion of laryngeal cancer that was never confirmed. For this patient, a laryngoscopy was performed, but there was no confirmation of cancer (data from the clinical database).

In 8 patients in the darolutamide + docetaxel + ADT arm and in 2 patients in the placebo + docetaxel + ADT arm subsequent systemic antineoplastic therapy was given for additional primary malignancies

- *mCRPC pool*

At least one TEAE was experienced by 94.2% of patients in the mCRPC pool.

TEAEs were of Grade 1 or Grade 2 as the worst grade in severity in the majority of the patients (64.2%). Grade 5 TEAEs were reported in 4.0% of patients.

TESAEs were reported in 28.3% of patients and TEAEs led to permanent discontinuation of the study drug in 7.5% of patients.

Similar to Study 17777, TEAEs of special topics were most commonly reported within the grouped term of fatigue/asthenic conditions in the mCRPC pool (32.4%). At the PT level, fatigue was also the most commonly reported TEAE in the mCRPC pool (26.0%)

Table 63 Incidences of TEAEs of special topics in mCRPC pool (SAF)

	Darolutamide
Grouped TEAE term [a]	N=173 n (%)
Fatigue/asthenic conditions	56 (32.4%)
Bone fractures (excluding pathological fractures)	9 (5.2%)
Fall	11 (6.4%)
Vasodilatation and flushing	12 (6.9%)
Breast disorders/gynecomastia	10 (5.8%)
Rash	12 (6.9%)
Hypertension	12 (6.9%)
Cardiac disorders	18 (10.4%)
Diabetes mellitus and hyperglycemia	3 (1.7%)
Mental impairment disorders	0
Depressed mood disorders	4 (2.3%)
Cerebral ischaemia	1 (0.6%)
Cerebral and intracranial hemorrhage	0
Seizure	1 (0.6%)
Weight decreased	13 (7.5%)

Abbreviations: 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

Note: The table contains counts of patients. If a patient experienced more than one episode of a TEAE, 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 in Module 5.3.5.1, IA mCRPC pool, Table 3.1/44.

MedDRA version 24.0.

Adverse drug reactions

For identification of ADRs of darolutamide in mHSPC indication, the clinical data from the Phase 3 Study 17777 (ARASENS) were analyzed.

The analysis of TEAEs and laboratory abnormalities for the identification of ADR was as follows:

- Selection of the TEAE preferred or grouped terms by evidence of disproportionality between the treatment arms: Selection of the TEAE preferred or grouped terms by evidence of disproportionality between the treatment arms (≥ 2%),
- Analysis of selected TEAE terms to identify further potential evidence: compatibility/consistency with the pharmacological properties of darolutamide such as mode of action, known pharmacological class effect, analysis of TEAEs over time, analysis of absolute and exposure-adjusted incidence rate,

- Assessment of relevance of the prioritized TEAE term/medical concept based on the frequency of ADR, proportion of SAEs, proportion of Grade ≥3 TEAEs, proportion of events leading to permanent discontinuation of study treatment or dose adjustment, analysis of baseline patient characteristics.

In addition to the analysis of TEAE terms, hematological and biochemical laboratory-based abnormalities were also reviewed, focusing on a higher incidence (≥5% difference) in the darolutamide + docetaxel + ADT arm compared to the placebo + docetaxel + ADT arm, central tendency (mean and median values), abnormal values distribution (categorized by severity grade) including shift-from-baseline analysis and laboratory-based abnormalities occurring with a difference in incidence between treatment arms of less than 5% were reviewed for clinical significance and considered in the context of the totality of safety data. (SmPC section 4.8)

Table 64 : Adverse reactions reported in mHSPC patients treated with darolutamide in combination with docetaxel in the ARASENS study a, b

System organ class (MedDRA)	Very common	Common
Vascular disorders	Hypertensionc	
Skin and subcutaneous tissue disorders	Rashd, e	
Musculoskeletal and connective tissue disorders		Fractures
Reproductive system and breast disorders		Gynaecomastia
Investigationsf	Neutrophil count decreased Blood bilirubin increased ALT increased AST increased	

a The median duration of exposure was 41.0 months (range: 0.1 to 56.5 months) in patients treated with darolutamide+docetaxel and 16.7 months (range: 0.3 to 55.8 months) in patients treated with placebo+docetaxel.
b Adverse reactions incidences may not be attributable to darolutamide alone but may contain contributions from other medicinal products used in combination.
c Includes hypertension, blood pressure increased, hypertensive emergency.
d Includes rash, drug eruption, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, erythema, dermatitis.
e The incidence was highest during the first 6 months of treatment.
f Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The incidence is based on values reported as laboratory abnormalities.

Serious adverse event/deaths/other significant events

- *Deaths*

Table 65 Overview of all deaths in Study 17777 (SAF)

Deaths Cause of death	Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
All deaths	**229 (35.1%)**	**304 (46.8%)**
Progressive disease	170 (26.1%)	234 (36.0%)
Adverse event not associated with clinical disease progression	22 (3.4%)	16 (2.5%)
Unknown	22 (3.4%)	26 (4.0%)
Other	13 (2.0%)	19 (2.9%)
Adverse event associated with clinical disease progression	2 (0.3%)	9 (1.4%)
Death from first to last dose of study drug	**1 (0.2%)**	**0**
Adverse event not associated with clinical disease progression	1 (0.2%)	0
Death within 30 days after last dose of study drug	**29 (4.4%)**	**27 (4.2%)**
Adverse event not associated with clinical disease progression	19 (2.9%)	10 (1.5%)
Progressive disease	5 (0.8%)	4 (0.6%)
Unknown	3 (0.5%)	5 (0.8%)
Adverse event associated with clinical disease progression	2 (0.3%)	7 (1.1%)
Other	0	1 (0.2%)
Death later than 30 days after last dose of study drug	**199 (30.5%)**	**277 (42.6%)**
Progressive disease	165 (25.3%)	230 (35.4%)
Unknown	19 (2.9%)	21 (3.2%)
Other	13 (2.0%)	18 (2.8%)
Adverse event not associated with clinical disease progression	2 (0.3%)	6 (0.9%)
Adverse event associated with clinical disease progression	0	2 (0.3%)

Abbreviations: N=Total number of patients (100%); n=Number of patients with event; SAF=Safety analysis set

A total of 229 patients (35.1%) in the darolutamide + docetaxel + ADT arm and 304 patients (46.8%) in the placebo + docetaxel + ADT arm had died as of the database cut-off date. The most common cause of death was progressive disease in both the darolutamide + docetaxel + ADT arm (26.1% of patients) and placebo + docetaxel + ADT arm (36.0% of patients).

The majority of deaths in the study occurred more than 30 days after the last dose of study drug in both the darolutamide + docetaxel + ADT arm (30.5% of patients) and the placebo + docetaxel + ADT arm (42.6% of patients).

No patients died before the treatment start. One patient in the darolutamide + docetaxel + ADT arm died during the treatment period due to an AE not associated with disease progression (acute cardiac failure reported on the same day when study drug was stopped).

A death within 30 days after the last dose of study drug was reported in 4.4% vs. 4.2% of patients in the darolutamide + docetaxel + ADT arm and placebo + docetaxel + ADT arm, respectively, mostly due to AEs not associated with disease progression (2.9% vs. 1.5%) or progressive disease (0.8% vs. 0.6%).

The incidences of all TEAEs with fatal outcome (Grade 5) are displayed in the table below.

Table 66 Incidence of all Grade 5 TEAEs by MedDRA PT in Study 17777 (SAF)

MedDRA PT v. 24.1	Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Any Grade 5 TEAE	**27 (4.1%)**	**26 (4.0%)**
COVID-19 pneumonia	4 (0.6%)	1 (0.2%)
Sudden death	2 (0.3%)	3 (0.5%)
General physical health deterioration	1 (0.2%)	4 (0.6%)
Cardiac arrest	1 (0.2%)	2 (0.3%)
Death	1 (0.2%)	2 (0.3%)
Hypoxia	1 (0.2%)	1 (0.2%)
Acute myocardial infarction	1 (0.2%)	0
Anaesthetic complication cardiac	1 (0.2%)	0
Arteriosclerosis	1 (0.2%)	0
COVID-19	1 (0.2%)	0
Cardiac disorder	1 (0.2%)	0
Cardiac failure acute	1 (0.2%)	0
Gastric cancer	1 (0.2%)	0
Haemoptysis	1 (0.2%)	0
Haemorrhagic stroke	1 (0.2%)	0
Hypertension	1 (0.2%)	0
Metastases to central nervous system	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0
Oesophageal carcinoma	1 (0.2%)	0
Parkinson's disease	1 (0.2%)	0
Pneumonitis	1 (0.2%)	0
Respiratory distress	1 (0.2%)	0
Septic shock	1 (0.2%)	0
Subarachnoid haemorrhage	1 (0.2%)	0
Transitional cell carcinoma	1 (0.2%)	0
Pneumonia	0	2 (0.3%)
Pulmonary sepsis	0	2 (0.3%)
Acute kidney injury	0	1 (0.2%)
Cachexia	0	1 (0.2%)
Cardiac failure	0	1 (0.2%)
Cerebrovascular accident	0	1 (0.2%)
Dyspnoea	0	1 (0.2%)
Gastric ulcer perforation	0	1 (0.2%)
Hypertransaminasaemia	0	1 (0.2%)
Interstitial lung disease	0	1 (0.2%)
Respiratory failure	0	1 (0.2%)
Sepsis	0	1 (0.2%)
Urinary bladder haemorrhage	0	1 (0.2%)

Abbreviations: COVID-19=Coronavirus disease 2019; 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; PT=Preferred term; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Notes:
A patient may have more than one entry.
Any adverse events with missing CTCAE grade are not included in this summary table.
CTCAE version 4.03.

- *Other serious adverse events (SAEs)*

An overview of treatment-emergent SAEs (TESAEs) that occurred in ≥1% of patients in either treatment arm in Study 17777 is presented in the table below.

Table 67 Incidence of TESAEs (any grade) by MedDRA PT occurring in ≥1% of patients in either treatment arm in Study 17777 (SAF)

	Darolutamide+ docetaxel arm N=652		Placebo+ docetaxel arm N=650	
MedDRA PT v. 24.1	Total n (%)	EAIR per 100 PY [a]	Total n (%)	EAIR per 100 PY [a]
Febrile neutropenia	40 (6.1%)	2.3	39 (6.0%)	3.2
Neutrophil count decreased	18 (2.8%)	1.0	10 (1.5%)	0.8
Pneumonia	16 (2.5%)	0.9	21 (3.2%)	1.7
Neutropenia	12 (1.8%)	0.7	14 (2.2%)	1.2
Pyrexia	9 (1.4%)	0.5	15 (2.3%)	1.2
COVID-19 pneumonia	7 (1.1%)	0.4	3 (0.5%)	0.2
Alanine aminotransferase increased	6 (0.9%)	0.3	8 (1.2%)	0.7
Urinary tract infection	6 (0.9%)	0.3	7 (1.1%)	0.6
Spinal cord compression	2 (0.3%)	0.1	7 (1.1%)	0.6

Abbreviations: COVID-19=Coronavirus disease 2019; EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of patients (100%); n=Number of patients with event; PT=Preferred term; PY=Patient year; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event; TESAE=Treatment-emergent serious adverse event

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

Note: A patient may have more than one entry.

In the ongoing Study 21140 in mHSPC patients receiving darolutamide or placebo in addition to ADT (based on non-validated clinical database), SAE was reported during treatment or within 30 days after study treatment discontinuation as of the database cut-off date for the submission (25 OCT 2021).

In the ongoing roll-over Study 20321 in patients receiving treatment with darolutamide in addition to ADT (based on non-validated clinical database), at least one SAE was reported in 38 patients during treatment or within 30 days after study treatment discontinuation as of the database cut-off date for the submission (25 OCT 2021). SAEs were most frequently reported in SOCs infections and infestations (14 events), renal and urinary disorders (8 events) and cardiac disorders (6 events).

Laboratory findings

- **Hematological and biochemical laboratory abnormalities**

Laboratory abnormalities at baseline were reported with a worst grade of 1 or 2 for most patients in both treatment arms. There were only a few laboratory abnormalities with a worst grade of 4: ALP increased in 1.7% of patients in the darolutamide + docetaxel + ADT arm vs. 2.9% of patients in the placebo + docetaxel + ADT arm, lymphocyte count decreased (0.8% vs. 0.2%), neutrophil count decreased (0.8% vs. 0%), hyperglycaemia (0.4% vs. 0%), and hyperkalaemia (0% vs. 0.2%). Overall, pre-treatment laboratory abnormalities were reported at similar incidences in both treatment arms.

The incidences of hematological and biochemical laboratory abnormalities in Study 17777 after the start of treatment are presented by CTCAE term and worst CTCAE grade in the table below.

Table 68 CTCAE grades for abnormal hematological and biochemical laboratory values in Study 17777: Worst grade after start of treatment (SAF)

Event category CTCAE term (version 4.03)	Darolutamide+ docetaxel arm n (%)						Placebo+ docetaxel arm n (%)					
		Worst CTCAE grade						Worst CTCAE grade				
	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	649 (100.0)	622 (95.8)	413 (63.6)	171 (26.3)	38 (5.9)	0	646 (100.0)	605 (93.7)	412 (63.8)	149 (23.1)	44 (6.8)	0
Leukocytosis	649 (100.0)	1 (0.2)	0	0	1 (0.2)	0	647 (100.0)	0	0	0	0	0
Investigations												
Alkaline phosphatase increased	646 (100.0)	405 (62.7)	264 (40.9)	76 (11.8)	62 (9.6)	3 (0.5)	644 (100.0)	409 (63.5)	235 (36.5)	97 (15.1)	66 (10.2)	11 (1.7)
White blood cell decreased	649 (100.0)	362 (55.8)	87 (13.4)	100 (15.4)	136 (21.0)	39 (6.0)	647 (100.0)	339 (52.4)	71 (11.0)	97 (15.0)	134 (20.7)	37 (5.7)
Lymphocyte count decreased	526 (100.0)	297 (56.5)	99 (18.8)	132 (25.1)	55 (10.5)	11 (2.1)	495 (100.0)	274 (55.4)	94 (19.0)	113 (22.8)	63 (12.7)	4 (0.8)
Aspartate aminotransferase increased	647 (100.0)	284 (43.9)	238 (36.8)	23 (3.6)	22 (3.4)	1 (0.2)	647 (100.0)	254 (39.3)	218 (33.7)	21 (3.2)	13 (2.0)	2 (0.3)
Neutrophil count decreased	543 (100.0)	275 (50.6)	42 (7.7)	46 (8.5)	67 (12.3)	120 (22.1)	516 (100.0)	235 (45.5)	32 (6.2)	41 (7.9)	62 (12.0)	100 (19.4)
Alanine aminotransferase increased	647 (100.0)	274 (42.3)	221 (34.2)	29 (4.5)	22 (3.4)	2 (0.3)	647 (100.0)	246 (38.0)	204 (31.5)	23 (3.6)	16 (2.5)	3 (0.5)
Platelet count decreased	649 (100.0)	170 (26.2)	149 (23.0)	11 (1.7)	9 (1.4)	1 (0.2)	646 (100.0)	161 (24.9)	143 (22.1)	7 (1.1)	9 (1.4)	2 (0.3)
Creatinine increased	647 (100.0)	163 (25.2)	130 (20.1)	26 (4.0)	3 (0.5)	4 (0.6)	645 (100.0)	161 (25.0)	127 (19.7)	28 (4.3)	5 (0.8)	1 (0.2)
Blood bilirubin increased	647 (100.0)	127 (19.6)	97 (15.0)	27 (4.2)	1 (0.2)	2 (0.3)	647 (100.0)	65 (10.0)	52 (8.0)	11 (1.7)	2 (0.3)	0
INR increased	214 (100.0)	32 (15.0)	20 (9.3)	8 (3.7)	4 (1.9)	0	197 (100.0)	39 (19.8)	25 (12.7)	9 (4.6)	5 (2.5)	0
Lymphocyte count increased	527 (100.0)	29 (5.5)	0	29 (5.5)	0	0	495 (100.0)	38 (7.7)	0	37 (7.5)	1 (0.2)	0
Hemoglobin increased	649 (100.0)	4 (0.6)	3 (0.5)	0	1 (0.2)	0	646 (100.0)	6 (0.9)	5 (0.8)	1 (0.2)	0	0
Metabolism and nutrition disorders												
Hyperglycemia	638 (100.0)	477 (74.8)	317 (49.7)	101 (15.8)	56 (8.8)	3 (0.5)	636 (100.0)	451 (70.9)	265 (41.7)	110 (17.3)	68 (10.7)	8 (1.3)
Hypoalbuminemia	645 (100.0)	259 (40.2)	204 (31.6)	51 (7.9)	4 (0.6)	0	642 (100.0)	275 (42.8)	215 (33.5)	58 (9.0)	2 (0.3)	0
Hypocalcemia	647 (100.0)	225 (34.8)	149 (23.0)	57 (8.8)	14 (2.2)	5 (0.8)	644 (100.0)	199 (30.9)	133 (20.7)	51 (7.9)	12 (1.9)	3 (0.5)
Hyponatremia	647 (100.0)	195 (30.1)	167 (25.8)	0	25 (3.9)	3 (0.5)	645 (100.0)	176 (27.3)	152 (23.6)	0	24 (3.7)	0
Hyperkalemia	647 (100.0)	168 (26.0)	124 (19.2)	34 (5.3)	10 (1.5)	0	645 (100.0)	132 (20.5)	106 (16.4)	20 (3.1)	5 (0.8)	1 (0.2)
Hypercalcemia	647 (100.0)	128 (19.8)	122 (18.9)	3 (0.5)	1 (0.2)	2 (0.3)	644 (100.0)	108 (16.8)	101 (15.7)	5 (0.8)	1 (0.2)	1 (0.2)
Hypokalemia	647 (100.0)	116 (17.9)	0	100 (15.5)	14 (2.2)	2 (0.3)	645 (100.0)	96 (14.9)	0	86 (13.3)	7 (1.1)	3 (0.5)
Hypernatremia	647 (100.0)	87 (13.4)	79 (12.2)	6 (0.9)	2 (0.3)	0	645 (100.0)	81 (12.6)	69 (10.7)	10 (1.6)	1 (0.2)	1 (0.2)
Hypoglycemia	645 (100.0)	46 (7.1)	40 (6.2)	5 (0.8)	1 (0.2)	0	644 (100.0)	41 (6.4)	35 (5.4)	6 (0.9)	0	0

Abbreviations: AE=Adverse event; CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of patients; n=Number of patients with event; SAF=Safety analysis set.
a: The number of patients with a specific laboratory value available. It does not include "not graded".
Notes:
A patient was considered at risk of the laboratory abnormality if the patient had a laboratory measurement for the particular laboratory abnormality.
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 abnormalities reported as AEs that include clinical assessments are presented 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.
CTCAE Version 4.03

Laboratory abnormalities that were reported with ≥5 percentage points higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm included **blood bilirubin increased** (19.6% vs. 10.0% of patients, respectively), **neutrophil count decreased** (50.6% vs. 45.5%), and **hyperkalaemia** (26.0% vs. 20.5%).

Analysis of liver function tests

- *Alanine aminotransferase (ALT)*

In Study 17777 at baseline, the median value was 24.00 U/L in both treatment arms. Before the start of study treatment, increased ALT (any grade) was reported as a laboratory abnormality in 11.4% of patients in the darolutamide + docetaxel + ADT arm and in 11.2% of patients in the placebo + docetaxel + ADT arm. No patients had pre-treatment abnormalities of Grade >2.

ALT increased was reported as a laboratory abnormality with a slightly higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm, i.e. 42.3% vs 38.0%. Most of the events were reported with a worst grade of 1 in both treatment arms (34.2% and 31.5% in the darolutamide + docetaxel + ADT arm and placebo + docetaxel + ADT arm respectively). Treatment-emergent laboratory abnormality of ALT increased with a worst grade of 3 was observed in 22 patients (3.4%) in the darolutamide + docetaxel + ADT arm vs. 16 patients (2.5%) in the placebo + docetaxel + ADT arm, and with a worst grade of 4 in 2 patients (0.3%) vs. 3 patients (0.5%), respectively.

ALT increased of any grade was reported as a TEAE in 15.6% of patients in the darolutamide + docetaxel + ADT arm and in 12.9% of patients in the placebo + docetaxel + ADT arm. TEAEs of Grade 3/4 ALT increased occurred in 18 patients (2.8%) in the darolutamide + docetaxel + ADT arm compared with 11 patients (1.7%) in the placebo + docetaxel + ADT arm.

- *Aspartate aminotransferase (AST)*

In Study 17777 at baseline, the median value was 24.00 U/L in both treatment arms. Before the start of study treatment, increased AST (any grade) was reported as a laboratory abnormality in 7.7% of patients in the darolutamide + docetaxel + ADT arm and in 8.6% of patients in the placebo + docetaxel + ADT arm. No patients had pre-treatment abnormalities of Grade >2.

AST increased was reported as a laboratory abnormality with a slightly higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm, i.e. 43.9% vs 39.3%. Most of the events were reported with a worst grade of 1 in both treatment arms (36.8% and 33.7% in the darolutamide + docetaxel + ADT arm and placebo + docetaxel + ADT arm respectively).

Treatment-emergent laboratory abnormality of AST increased with a1 worst grade of 3 was observed in 22 patients (3.4%) in the darolutamide + docetaxel + ADT arm vs. 13 patients (2.0%) in the placebo + docetaxel + ADT arm, and with a worst grade of 4 in 1 patient (0.2%) vs. 2 patients (0.3%), respectively.

AST increased of any grade was reported as a TEAE in 14.0% of patients in the darolutamide + docetaxel + ADT arm and in 10.5% of patients in the placebo + docetaxel + ADT arm. TEAEs of Grade 3/4 AST increased occurred in 17 patients (2.6%) in the darolutamide + docetaxel + ADT arm compared with 7 patients (1.1%) in the placebo + docetaxel + ADT arm

- *Alkaline phosphatase (ALP)*

ALP increased was reported as a laboratory abnormality with comparable incidences in both treatment arms (62.7% and 63.5% in darolutamide + docetaxel + ADT arm and in the placebo + docetaxel + ADT arm, respectively). Most of the events were reported with a worst grade of 1 or 2 in both

treatment arms. Blood ALP increased was reported as a TEAE in 6.9% of patients in the darolutamide + docetaxel + ADT arm and in 6.6% of patients in the placebo + docetaxel + ADT arm.

- *Blood bilirubin*

Before the start of study treatment, laboratory abnormality of blood bilirubin increased was observed at a similar incidence in the darolutamide + docetaxel + ADT arm (1.5%) and the placebo + docetaxel + ADT arm (1.1%).

Blood bilirubin increased was observed with a higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm. Most of the events were reported with a worst grade of 1 or 2 in both treatment arms, i.e. all grade 19.6% vs. 10.0% in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively; Grade 1: 15.0% vs. 8.0% and Grade 2: 4.2% vs. 1.7%. Overall, increases in worst grade from pre-treatment were observed at a higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm.

The difference in bilirubin between the treatment arms over time increased after the 6 months of docetaxel combination treatment period.

Blood bilirubin increased (part of SOC of investigations) was reported as a TEAE in 4.9% of patients in the darolutamide + docetaxel + ADT arm and in 2.9% of patients in the placebo + docetaxel + ADT arm. Almost all patients with TEAE blood bilirubin increased had events with a worst grade of 1 or 2, and there was 1 patient (0.2%) in the darolutamide + docetaxel + ADT arm with an event with a worst grade of 3 (no patients in the placebo + docetaxel + ADT arm). Hyperbilirubinemia (part of SOC of hepatobiliary disorders) was reported as a TEAE in 2 patients (0.3%) in the placebo + docetaxel + ADT arm (1 patient had an event with a worst grade of 1 and 1 patient with a worst grade of 3) (no patients in the darolutamide + docetaxel + ADT arm).

Hy's Law and drug-induced liver injury (DILI)

Potential Hy's Law cases

Possible Hy's Law cases were defined as patients with treatment-emergent abnormalities of liver function tests falling in the Hy's Law range (patients with elevated AST and/or ALT >3xULN, and bilirubin ≥2xULN) with ALP <2xULN. Two cases in darolutamide+docetaxel arm and two cases in the placebo+docetaxel arm. One case in the darolutamide+docetaxel arm experienced hepatocellular injury meeting Hy's Law criteria 37 days after commencing darolutamide treatment and 13 days after the first and only dose of docetaxel. Marked increases in ALT and AST occurred with evidence of hepatic functional impairment as indicated by concurrent elevated bilirubin and INR. Skin rash and pyrexia were also documented.

Increase in transaminases

The incidence was 17.6% and 14.9%, respectively, in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm. Worst Grade 3 TEAEs occurred in 3.4% of patients in the darolutamide + docetaxel + ADT arm vs. 1.8% of patients in the placebo + docetaxel + ADT arm. TEAEs of increase in transaminases (MLG) with a worst grade of 4 occurred in 1 patient (0.2%) in the darolutamide + docetaxel + ADT arm and 2 patients (0.3%) in the placebo + docetaxel + ADT arm. This patient had reversible and clinically asymptomatic increases in ALT and AST of >20xULN with concurrent normal bilirubin levels Docetaxel had been discontinued almost 5 months prior to the events. Dechallenge and rechallenge with darolutamide was positive.

Drug-induced liver injury (DILI), PT (part of SOC of hepatobiliary disorders): TEAEs occurred in 3 patients (0.5%) in the darolutamide + docetaxel + ADT arm and 4 patients (0.6%) in the placebo + docetaxel + ADT arm. In the darolutamide + docetaxel + ADT arm, 2 cases were Grade 2 and one

case was Grade 4. In the place+docetaxel arm, one case was Grade 1, 2 cases were Grade 2 and one case was Grade 3.

Of the 7 patients, 3 patients in the placebo + docetaxel + ADT arm had non-serious TEAEs of DILI, all with isolated transaminase elevations and no meaningful increase in total bilirubin level.

The remaining 4 patients experienced TESAEs of DILI (3 patients in the darolutamide + docetaxel + ADT arm and 1 patient in the placebo + docetaxel + ADT arm). One of the patients in the darolutamide + docetaxel + ADT arm who had a DILI TESAE with a worst grade of 4 is discussed above as one of the potential Hy's Law cases.

12-lead ECG and QTc

At Screening, the 12-lead ECG was performed for 633/652 (97.1%) and 607/650 (93.4%) patients in the darolutamide + docetaxel + ADT and placebo + docetaxel + ADT arm, respectively, of which 43.4% and 41.7% of patients had central ECG reading interpreted as abnormal (of which 1.5% and 1.4%, respectively, were considered clinically significant by the investigator). The analysis of the ECG data by visit did not reveal any relevant imbalance between the treatment arms or changes from baseline.

A summary of QTcF values at baseline, at EOT, and at last visit is presented in the table below.

Table 69 Summary of QTcF values in Study 17777 (SAF)

	Darolutamide+ docetaxel arm N=652			Placebo+ docetaxel arm N=650		
Number of patients (%) with:	Baseline N=642	End of treatment N=219	Last visit N=651	Baseline N=636	End of treatment N=377	Last visit N=647
Value <=450 msec	561 (87.4)	191 (87.2)	563 (86.5)	554 (87.1)	330 (87.5)	559 (86.4)
Value 451 - 480 msec	68 (10.6)	17 (7.8)	71 (10.9)	68 (10.7)	40 (10.6)	73 (11.3)
Value 481 - 500 msec	11 (1.7)	4 (1.8)	7 (1.1)	8 (1.3)	3 (0.8)	8 (1.2)
Value >500 msec	2 (0.3)	7 (3.2)	10 (1.5)	6 (0.9)	4 (1.1)	7 (1.1)
Increase >30-60 msec from baseline	0	12 (5.5)	36 (5.5)	0	23 (6.1)	39 (6.0)
Increase >60 msec from baseline	0	6 (2.7)	10 (1.5)	0	4 (1.1)	10 (1.5)

	Darolutamide+ docetaxel arm N=652		Placebo+ docetaxel arm N=650	
At any time during study	n (%)	EAIR (per 100 patient years)	n (%)	EAIR (per 100 patient years)
QTcF >500 msec	50 (7.7)	2.9	39 (6.0)	3.2

Abbreviations: EAIR=Exposure-adjusted incidence rate; N=Total number of patients (100%); n=Number of patients with event; QTcF=Corrected QT (Fridericia's formulae); SAF=Safety analysis set

Among the 7 patients with a post baseline QTcF value >500 msec at the EOT visit in the darolutamide + docetaxel + ADT arm, most of them had this value only at the EOT visit and not in prior visits.

TEAE electrocardiogram QT prolonged was reported in 5 patients (0.8%) in the darolutamide + docetaxel + ADT arm and in 7 patients (1.1%) in the placebo + docetaxel + ADT arm. All these were reported as non-serious and the study drug doses were not modified due to the events in any of the patients.

Fridericia QTc results were in general similar between treatments arms, and within a treatment arm, at baseline, end of treatment, and last visit. Baseline ECG abnormalities were observed at a similar incidence in patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm. An analysis of ECG data over time did not reveal any relevant imbalance between the treatment arms.

Safety in special populations

Subgroup analyses for TEAEs were performed for age, geographical region, renal function at baseline, hepatic function at baseline and concomitant statin use.

Age

An overview of TEAEs by age groups (<65, 65–74, 75–84, and ≥85 years) is presented in the table below.

Table 70 Overview of TEAEs by age in Study 17777 (SAF)

		Darolutamide+ docetaxel arm				Placebo+ docetaxel arm			
		Age (years)				Age (years)			
		<65	65–74	75–84	≥85	<65	65–74	75–84	≥85
Number of patients (%) with:		N=243 n (%)	N=303 n (%)	N=103 n (%)	N=3 n (%)	N=232 n (%)	N=305 n (%)	N=109 n (%)	N=4 n (%)
Any TEAE		**242 (99.6)**	**302 (99.7)**	**102 (99.0)**	**3 (100.0)**	**230 (99.1)**	**301 (98.7)**	**108 (99.1)**	**4 (100.0)**
Worst grade:	Grade 1	14 (5.8)	10 (3.3)	4 (3.9)	0	20 (8.6)	13 (4.3)	2 (1.8)	0
	Grade 2	84 (34.6)	60 (19.8)	18 (17.5)	0	62 (26.7)	88 (28.9)	19 (17.4)	0
	Grade 3	83 (34.2)	127 (41.9)	37 (35.9)	1 (33.3)	92 (39.7)	102 (33.4)	37 (33.9)	1 (25.0)
	Grade 4	51 (21.0)	92 (30.4)	38 (36.9)	2 (66.7)	53 (22.8)	87 (28.5)	39 (35.8)	2 (50.0)
	Grade 5	10 (4.1)	12 (4.0)	5 (4.9)	0	3 (1.3)	11 (3.6)	11 (10.1)	1 (25.0)
	Missing	0	1 (0.3)	0	0	0	0	0	0
Serious TEAE		**82 (33.7)**	**152 (50.2)**	**55 (53.4)**	**3 (100.0)**	**89 (38.4)**	**125 (41.0)**	**58 (53.2)**	**3 (75.0)**
Fatal (Grade 5)		10 (4.1)	12 (4.0)	5 (4.9)	0	3 (1.3)	11 (3.6)	11 (10.1)	1 (25.0)
Requires or prolongs hospitalization		76 (31.3)	143 (47.2)	52 (50.5)	3 (100.0)	82 (35.3)	118 (38.7)	56 (51.4)	3 (75.0)
Life-threatening		6 (2.5)	13 (4.3)	4 (3.9)	1 (33.3)	3 (1.3)	15 (4.9)	7 (6.4)	2 (50.0)
Disability/incapacity		2 (0.8)	1 (0.3)	0	0	4 (1.7)	4 (1.3)	0	0
Other (medically significant)		9 (3.7)	17 (5.6)	4 (3.9)	1 (33.3)	8 (3.4)	10 (3.3)	4 (3.7)	0
TEAE leading to study drug dose modification [a]		56 (23.0)	87 (28.7)	24 (23.3)	2 (66.7)	25 (10.8)	60 (19.7)	26 (23.9)	1 (25.0)
TEAE leading to permanent discontinuation of study drug		31 (12.8)	41 (13.5)	14 (13.6)	2 (66.7)	17 (7.3)	32 (10.5)	19 (17.4)	1 (25.0)
TEAE leading to docetaxel dose modification [a]		68 (28.0)	108 (35.6)	37 (35.9)	1 (33.3)	64 (27.6)	101 (33.1)	46 (42.2)	3 (75.0)
TEAE leading to permanent discontinuation of docetaxel		11 (4.5)	28 (9.2)	12 (11.7)	1 (33.3)	11 (4.7)	33 (10.8)	23 (21.1)	0
Specific categories									
Psychiatric disorders (SOC)		45 (18.5)	55 (18.2)	12 (11.7)	2 (66.7)	50 (21.6)	54 (17.7)	22 (20.2)	0
Nervous system disorders (SOC)		121 (49.8)	163 (53.8)	58 (56.3)	2 (66.7)	113 (48.7)	172 (56.4)	55 (50.5)	2 (50.0)
Accidents and injuries (SMQ)		38 (15.6)	50 (16.5)	22 (21.4)	1 (33.3)	33 (14.2)	47 (15.4)	11 (10.1)	1 (25.0)
Cardiac disorders (SOC)		25 (10.3)	43 (14.2)	14 (13.6)	1 (33.3)	25 (10.8)	47 (15.4)	17 (15.6)	1 (25.0)
Vascular disorders (SOC)		93 (38.3)	116 (38.3)	33 (32.0)	1 (33.3)	91 (39.2)	99 (32.5)	43 (39.4)	0
Central nervous system vascular disorders (SMQ)		4 (1.6)	17 (5.6)	3 (2.9)	0	6 (2.6)	9 (3.0)	4 (3.7)	0
Infections and infestations (SOC)		120 (49.4)	153 (50.5)	45 (43.7)	2 (66.7)	101 (43.5)	150 (49.2)	55 (50.5)	3 (75.0)
Anticholinergic syndrome (SMQ) [b]		2 (0.8)	2 (0.7)	1 (1.0)	0	0	0	1 (0.9)	0
Quality of life decreased (PT)		0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures		42 (17.3)	70 (23.1)	26 (25.2)	2 (66.7)	36 (15.5)	52 (17.0)	27 (24.8)	0

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; EMA=European Medicines Agency; 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; SMQ=Standardized MedDRA Query; SOC=System organ class; TEAE=Treatment-emergent adverse event

a: Modifications include dose interruption/delay and reductions.

b: The algorithm approach is used per MedDRA guidance of the SMQ Anticholinergic syndrome.

Notes: 'Any TEAE' also includes patients with grade not available for all adverse events.

CTCAE version 4.03. MedDRA version 24.1.

Geographical region

Table 71 Overview of TEAEs by geographical region in Study 17777 (SAF)

		Darolutamide+ docetaxel arm			Placebo+ docetaxel arm		
		Geographical region			Geographical region		
		North America	Asia Pacific	ROW	North America	Asia Pacific	ROW
		N=125	N=230	N=297	N=117	N=242	N=291
Number of patients (%) with		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE		125 (100.0)	229 (99.6)	295 (99.3)	116 (99.1)	239 (98.8)	288 (99.0)
Worst grade:	Grade 1	5 (4.0)	4 (1.7)	19 (6.4)	4 (3.4)	8 (3.3)	23 (7.9)
	Grade 2	37 (29.6)	31 (13.5)	94 (31.6)	33 (28.2)	44 (18.2)	92 (31.6)
	Grade 3	49 (39.2)	75 (32.6)	124 (41.8)	55 (47.0)	69 (28.5)	108 (37.1)
	Grade 4	27 (21.6)	110 (47.8)	46 (15.5)	23 (19.7)	113 (46.7)	45 (15.5)
	Grade 5	7 (5.6)	8 (3.5)	12 (4.0)	1 (0.9)	5 (2.1)	20 (6.9)
	Missing	0	1 (0.4)	0	0	0	0
TESAE		55 (44.0)	121 (52.6)	116 (39.1)	44 (37.6)	110 (45.5)	121 (41.6)
TEAE leading to study drug dose modification [a]		41 (32.8)	55 (23.9)	73 (24.6)	27 (23.1)	34 (14.0)	51 (17.5)
TEAE leading to permanent discontinuation of study drug		22 (17.6)	30 (13.0)	36 (12.1)	11 (9.4)	19 (7.9)	39 (13.4)
TEAE leading to docetaxel dose modification [a]		34 (27.2)	117 (50.9)	63 (21.2)	33 (28.2)	116 (47.9)	65 (22.3)
TEAE leading to permanent discontinuation of docetaxel		10 (8.0)	27 (11.7)	15 (5.1)	11 (9.4)	28 (11.6)	28 (9.6)

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of patients (100%); n=Number of patients with event; ROW=Rest of the world; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event TESAE=Treatment-emergent serious adverse event
a: Modifications include dose interruption/delay and reductions.
Note: 'Any TEAE' also includes patients with grade not available for all adverse events.
CTCAE version 4.03.

Renal function at baseline

Table 72 Overview of TEAEs by renal function at baseline in Study 17777 (SAF)

	Darolutamide+ docetaxel arm				Placebo+ docetaxel arm			
	eGFR at baseline				eGFR at baseline			
	Normal	Mild impairment	Moderate impairment	Severe impairment	Normal	Mild impairment	Moderate impairment	Severe impairment
Number of patients (%) with	N=376 n (%)	N=236 n (%)	N=39 n (%)	N=1 [a] n (%)	N=362 n (%)	N=234 n (%)	N=53 n (%)	N=0 n (%)
Any TEAE	374 (99.5)	235 (99.6)	39 (100.0)	1 (100.0)	357 (98.6)	232 (99.1)	53 (100.0)	0
Worst grade: Grade 1	12 (3.2)	15 (6.4)	1 (2.6)	0	24 (6.6)	10 (4.3)	1 (1.9)	0
Grade 2	94 (25.0)	57 (24.2)	11 (28.2)	0	105 (29.0)	54 (23.1)	10 (18.9)	0
Grade 3	141 (37.5)	89 (37.7)	17 (43.6)	1 (100.0)	123 (34.0)	87 (37.2)	21 (39.6)	0
Grade 4	110 (29.3)	66 (28.0)	7 (17.9)	0	95 (26.2)	71 (30.3)	15 (28.3)	0
Grade 5	16 (4.3)	8 (3.4)	3 (7.7)	0	10 (2.8)	10 (4.3)	6 (11.3)	0
Missing	1 (0.3)	0	0	0	0	0	0	0
TESAE	162 (43.1)	111 (47.0)	18 (46.2)	1 (100.0)	146 (40.3)	100 (42.7)	28 (52.8)	0
TEAE leading to study drug dose modification [b]	83 (22.1)	72 (30.5)	13 (33.3)	1 (100.0)	45 (12.4)	48 (20.5)	18 (34.0)	0
TEAE leading to permanent discontinuation of study drug	47 (12.5)	34 (14.4)	6 (15.4)	1 (100.0)	33 (9.1)	23 (9.8)	12 (22.6)	0
TEAE leading to docetaxel dose modification [b]	131 (34.8)	70 (29.7)	13 (33.3)	0	110 (30.4)	81 (34.6)	23 (43.4)	0
TEAE leading to permanent discontinuation of docetaxel	30 (8.0)	18 (7.6)	4 (10.3)	0	36 (9.9)	22 (9.4)	9 (17.0)	0

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; eGFR=Estimated glomerular filtration rate; N=total number of patients (100%); n=Number of patients with event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event; TESAE=Treatment-emergent serious adverse event; ULN=Upper limit of normal
a: One patient had severe renal impairment at baseline based on eGFR but was eligible based on a serum creatinine level below ≤2.0 x ULN (Module 5.3.5.1, Report PH-42024, Listing 16.2.4/5).
b: Modifications include dose interruption/delay and reductions.
Notes: Patients with missing renal function information at baseline are not included in this table.
'Any TEAE' also includes patients with grade not available for all adverse events.
CTCAE version 4.03

Hepatic function at baseline

Table 73 Overview of TEAEs by hepatic function at baseline in Study 17777 (SAF)

		Darolutamide+ docetaxel arm			Placebo+ docetaxel arm		
		Hepatic function at baseline			Hepatic function at baseline		
		Normal	Mild impairment	Moderate impairment	Normal	Mild impairment	Moderate impairment
		N=598	N=49	N=2	N=589	N=52	N=0
Number of patients (%) with		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE		**595 (99.5)**	**49 (100.0)**	**2 (100.0)**	**583 (99.0)**	**51 (98.1)**	**0**
Worst grade:	Grade 1	26 (4.3)	2 (4.1)	0	33 (5.6)	2 (3.8)	0
	Grade 2	146 (24.4)	15 (30.6)	0	155 (26.3)	14 (26.9)	0
	Grade 3	230 (38.5)	16 (32.7)	1 (50.0)	204 (34.6)	21 (40.4)	0
	Grade 4	167 (27.9)	14 (28.6)	1 (50.0)	169 (28.7)	10 (19.2)	0
	Grade 5	25 (4.2)	2 (4.1)	0	22 (3.7)	4 (7.7)	0
	Missing	1 (0.2)	0	0	0	0	0
TESAE		270 (45.2)	21 (42.9)	1 (50.0)	240 (40.7)	28 (53.8)	0
TEAE leading to study drug dose modification [a]		155 (25.9)	12 (24.5)	2 (100.0)	95 (16.1)	14 (26.9)	0
TEAE leading to permanent discontinuation of study drug		82 (13.7)	5 (10.2)	1 (50.0)	61 (10.4)	7 (13.5)	0
TEAE leading to docetaxel dose modification [a]		196 (32.8)	18 (36.7)	0	192 (32.6)	18 (34.6)	0
TEAE leading to permanent discontinuation of docetaxel		47 (7.9)	5 (10.2)	0	63 (10.7)	4 (7.7)	0

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of patients (100%); n=Number of patients with event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event TESAE=Treatment-emergent serious adverse event
a: Modifications include dose interruption/delay and reductions.
Notes: Patients with missing hepatic function information at baseline are not included in this table.
'Any TEAE' also includes patients with grade not available for all adverse events.
CTCAE version 4.03

Concomitant statin use

Concomitant use of statins with darolutamide can increase the exposure to statins, with rosuvastatin increasing up to 5-fold (Zurth et al. 2019). Therefore, a subgroup analysis was performed to investigate whether the AE profile differs between users and non-users of statins. This analysis included all TEAEs that were reported in concomitant statin users compared with non-users regardless of the time when the event occurred (ie, not considering if the event occurred during concomitant darolutamide and statin administration). An overview of TEAEs by concomitant statin use in Study 17777 is presented below.

Table 74 Overview of TEAEs by concomitant statin use in Study 17777 (SAF)

		Darolutamide+ docetaxel arm		Placebo+ docetaxel arm	
		Concomitant statin use		Concomitant statin use	
		No	Yes	No	Yes
		N=469	N=183	N=480	N=170
Number of patients (%) with		n (%)	n (%)	n (%)	n (%)
Any TEAE		**467 (99.6%)**	**182 (99.5%)**	**473 (98.5%)**	**170 (100.0%)**
Worst grade:	Grade 1	18 (3.8%)	10 (5.5%)	30 (6.3%)	5 (2.9%)
	Grade 2	120 (25.6%)	42 (23.0%)	126 (26.3%)	43 (25.3%)
	Grade 3	178 (38.0%)	70 (38.3%)	173 (36.0%)	59 (34.7%)
	Grade 4	131 (27.9%)	52 (28.4%)	121 (25.2%)	60 (35.3%)
	Grade 5	19 (4.1%)	8 (4.4%)	23 (4.8%)	3 (1.8%)
	Missing	1 (0.2%)	0	0	0
TESAE		190 (40.5%)	102 (55.7%)	190 (39.6%)	85 (50.0%)
TEAE leading to study drug dose modification [a]		111 (23.7%)	58 (31.7%)	75 (15.6%)	37 (21.8%)
TEAE leading to permanent discontinuation of study drug		66 (14.1%)	22 (12.0%)	53 (11.0%)	16 (9.4%)
TEAE leading to docetaxel dose modification [a]		147 (31.3%)	67 (36.6%)	146 (30.4%)	68 (40.0%)
TEAE leading to permanent discontinuation of docetaxel		32 (6.8%)	20 (10.9%)	48 (10.0%)	19 (11.2%)

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of patients (100%); n=Number of patients with event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event TESAE=Treatment-emergent serious adverse event
a: Modifications include dose interruption/delay and reductions.
Note: 'Any TEAE' also includes patients with grade not available for all adverse events.
CTCAE version 4.03

Discontinuation due to adverse events

- *TEAEs leading to permanent discontinuation*

Overall, TEAEs that resulted in permanent **discontinuation of study drug** occurred at a higher incidence in the darolutamide + docetaxel + ADT arm than the placebo + docetaxel + ADT arm (13.5% vs. 10.6%, respectively). The most common TEAEs leading to permanent discontinuation of study drug (in ≥5 patients in either treatment arm) were AST increased (0.9% vs. 0.3%), ALT increased (0.8% vs. 0.2%) and bone pain (0.3% vs. 1.4%).

The incidences of TEAEs that resulted in permanent **discontinuation of docetaxel** were slightly lower in the darolutamide + docetaxel + ADT arm compared to the placebo + docetaxel + ADT arm (8.0% vs. 10.3%, respectively). The most common TEAEs leading to permanent discontinuation of docetaxel (in ≥5 patients in either treatment arm) were neutrophil count decreased (0.8% vs. 0.5%), febrile neutropenia (0.5% vs. 0.8%), neutropenia (0.5% vs. 0.8%), and WBC count decreased (0.2% vs. 0.9%).

Table 75 Incidence of TEAEs leading to permanent discontinuation of study drug or docetaxel in Study 17777 (SAF)

		Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Any TEAE leading to discontinuation of study drug		**88 (13.5%)**	**69 (10.6%)**
Worst CTCAE grade:	Grade 1	8 (1.2%)	4 (0.6%)
	Grade 2	16 (2.5%)	20 (3.1%)
	Grade 3	38 (5.8%)	22 (3.4%)
	Grade 4	7 (1.1%)	7 (1.1%)
	Grade 5	19 (2.9%)	16 (2.5%)
TEAEs (any grade) occurring in ≥0.5% of patients in either treatment arm by MedDRA PT (v. 24.1)			
Aspartate aminotransferase increased		6 (0.9%)	2 (0.3%)
Alanine aminotransferase increased		5 (0.8%)	1 (0.2%)
COVID-19 pneumonia		4 (0.6%)	1 (0.2%)
Rash maculo-papular		3 (0.5%)	0
Bone pain		2 (0.3%)	9 (1.4%)
Back pain		2 (0.3%)	3 (0.5%)
Interstitial lung disease		1 (0.2%)	3 (0.5%)
Pneumonia		1 (0.2%)	3 (0.5%)
Any TEAE leading to discontinuation of docetaxel		**52 (8.0%)**	**67 (10.3%)**
Worst CTCAE grade:	Grade 1	8 (1.2%)	6 (0.9%)
	Grade 2	18 (2.8%)	21 (3.2%)
	Grade 3	17 (2.6%)	27 (4.2%)
	Grade 4	7 (1.1%)	8 (1.2%)
	Grade 5	2 (0.3%)	5 (0.8%)
TEAEs (any grade) occurring in ≥0.5% of patients in either treatment arm by MedDRA PT (v. 24.1)			
Neutrophil count decreased		5 (0.8%)	3 (0.5%)
Peripheral sensory neuropathy		4 (0.6%)	1 (0.2%)
Febrile neutropenia		3 (0.5%)	5 (0.8%)
Neutropenia		3 (0.5%)	5 (0.8%)
Malaise		3 (0.5%)	4 (0.6%)
Pneumonia		3 (0.5%)	4 (0.6%)
Alanine aminotransferase increased		3 (0.5%)	2 (0.3%)
Fatigue		2 (0.3%)	3 (0.5%)
Oedema peripheral		2 (0.3%)	3 (0.5%)
White blood cell count decreased		1 (0.2%)	6 (0.9%)
Aspartate aminotransferase increased		1 (0.2%)	3 (0.5%)
Dyspnoea		1 (0.2%)	3 (0.5%)
Interstitial lung disease		1 (0.2%)	3 (0.5%)
Anaemia		0	3 (0.5%)
Pulmonary embolism		0	3 (0.5%)

Abbreviations: COVID-19=Coronavirus disease 2019; 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; 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.

- *TEAEs leading to dose interruption*

TEAEs that resulted in **interruption of study drug** occurred at a higher incidence in the darolutamide + docetaxel + ADT arm (22.9%) than in the placebo + docetaxel + ADT+ ADT arm (15.7%). The most common TEAEs leading to interruption of study drug (in ≥2% of patients in either treatment arm) were ALT increased (3.2% vs. 1.5%), AST increased (3.1% vs. 1.1%), and febrile neutropenia (2.1% vs. 1.4%) in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. When adjusted for the difference in study drug treatment duration, the incidences of all TEAEs were comparable between the treatment arms, except for ALT increased (EAIRs of 1.2 vs. 0.8 per 100 PYs in the darolutamide + docetaxel + ADT and placebo + docetaxel + ADT arms, respectively), and AST increased (EAIRs of 1.2 vs. 0.6 per 100 PYs, respectively).

TEAEs that resulted in **interruption of docetaxel** occurred at a similar incidence between the treatment arms, in 21.9% of patients in the darolutamide + docetaxel + ADT arm and 20.6% of patients in the placebo + docetaxel + ADT arm. The most common TEAEs leading to interruption of docetaxel (in ≥2% of patients in either treatment arm) were ALT increased (4.0% vs. 3.4%), neutrophil count decreased (2.8% vs. 2.3%), and AST increased (2.8% vs. 1.7%) in the darolutamide + docetaxel + ADT arm and placebo + docetaxel + ADT arm, respectively.

Table 76 Incidence of TEAEs leading to interruption of study drug or docetaxel in Study 17777 (SAF)

		Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Any TEAE leading to interruption of study drug		**149 (22.9%)**	**102 (15.7%)**
Worst CTCAE grade:	Grade 1	6 (0.9%)	10 (1.5%)
	Grade 2	34 (5.2%)	18 (2.8%)
	Grade 3	92 (14.1%)	53 (8.2%)
	Grade 4	17 (2.6%)	21 (3.2%)
	Grade 5	0	0
TEAEs (any grade) occurring in ≥1% of patients in either treatment arm by MedDRA PT (v. 24.1)			
Alanine aminotransferase increased		21 (3.2%)	10 (1.5%)
Aspartate aminotransferase increased		20 (3.1%)	7 (1.1%)
Febrile neutropenia		14 (2.1%)	9 (1.4%)
Any TEAE leading to interruption of docetaxel		**143 (21.9%)**	**134 (20.6%)**
Worst CTCAE grade:	Grade 1	28 (4.3%)	29 (4.5%)
	Grade 2	58 (8.9%)	47 (7.2%)
	Grade 3	41 (6.3%)	43 (6.6%)
	Grade 4	16 (2.5%)	15 (2.3%)
	Grade 5	0	0
TEAEs (any grade) occurring in ≥1% of patients in either treatment arm by MedDRA PT (v. 24.1)			
Alanine aminotransferase increased		26 (4.0%)	22 (3.4%)
Neutrophil count decreased		18 (2.8%)	15 (2.3%)
Aspartate aminotransferase increased		18 (2.8%)	11 (1.7%)
Oedema peripheral		10 (1.5%)	5 (0.8%)
Neutropenia		8 (1.2%)	10 (1.5%)
White blood cell count decreased		8 (1.2%)	6 (0.9%)
Febrile neutropenia		7 (1.1%)	6 (0.9%)
Malaise		7 (1.1%)	3 (0.5%)
Blood bilirubin increased		5 (0.8%)	7 (1.1%)

Abbreviations: 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; 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.

- *TEAEs leading to dose reduction*

TEAEs that resulted in **dose reduction of study drug** occurred at a higher incidence in the darolutamide + docetaxel + ADT arm (8.7%) than in the placebo + docetaxel + ADT arm (4.3%). The most common TEAEs leading to dose reduction of study drug (in ≥2% of patients in either treatment

arm) were ALT increased (2.8% vs. 1.2%) and AST increased (2.5% vs. 0.8%) in the darolutamide + docetaxel + ADT arm and placebo + docetaxel + ADT arm, respectively. All other TEAEs were reported in ≤4 patients each. When adjusted for the difference in treatment duration, the incidences of all TEAEs were comparable between the treatment arms, except for AST increased, for which the EAIRs were 0.9 vs. 0.4 per 100 PYs in the darolutamide + docetaxel + ADT and placebo + docetaxel + ADT arms, respectively.

TEAEs that resulted in **dose reduction of docetaxel** occurred at a similar incidence between the treatment arms, in 19.9% of patients in the darolutamide + docetaxel + ADT arm and 19.5% of patients in the placebo + docetaxel + ADT arm. The most common TEAEs leading to reduction of docetaxel (in ≥2% of patients in either treatment arm) were neutrophil count decreased (5.4% vs. 6.0%), febrile neutropenia (3.7% vs. 3.8%), WBC count decreased (3.2% vs. 3.4%), and neutropenia (1.8% vs. 2.2%) in the darolutamide + docetaxel + ADT arm and placebo + docetaxel + ADT arm, respectively. The incidences of these TEAEs were comparable between the treatment arms.

Table 77 Incidence of TEAEs leading to dose reduction of study drug or docetaxel in Study 17777 (SAF)

		Darolutamide+ docetaxel arm N=652 n (%)	Placebo+ docetaxel arm N=650 n (%)
Any TEAE leading to study drug dose reduction		**57 (8.7%)**	**28 (4.3%)**
Worst CTCAE grade:	Grade 1	18 (2.8%)	9 (1.4%)
	Grade 2	22 (3.4%)	13 (2.0%)
	Grade 3	15 (2.3%)	6 (0.9%)
	Grade 4	2 (0.3%)	0
	Grade 5	0	0
TEAEs (any grade) occurring in ≥1% of patients in either treatment arm by MedDRA PT (v. 24.1)			
Alanine aminotransferase increased		18 (2.8%)	8 (1.2%)
Aspartate aminotransferase increased		16 (2.5%)	5 (0.8%)
Any TEAE leading to docetaxel dose reduction		**130 (19.9%)**	**127 (19.5%)**
Worst CTCAE grade:	Grade 1	16 (2.5%)	15 (2.3%)
	Grade 2	29 (4.4%)	28 (4.3%)
	Grade 3	54 (8.3%)	41 (6.3%)
	Grade 4	31 (4.8%)	43 (6.6%)
	Grade 5	0	0
TEAEs (any grade) occurring in ≥1% of patients in either treatment arm by MedDRA PT (v. 24.1)			
Neutrophil count decreased		35 (5.4%)	39 (6.0%)
Febrile neutropenia		24 (3.7%)	25 (3.8%)
White blood cell count decreased		21 (3.2%)	22 (3.4%)
Neutropenia		12 (1.8%)	14 (2.2%)
Myalgia		8 (1.2%)	4 (0.6%)

Abbreviations: 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; 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.

Post marketing experience

No new safety concerns were identified from darolutamide post-marketing surveillance between the first marketing authorization (30 JUL 2019) and the cut-off date for the latest Periodic Benefit-Risk Evaluation Report (PBRER) (30 JUL 2021).

From 30 JUL 2019 until 30 JUL 2021, the distributed volume of darolutamide (NUBEQA) 300 mg film-coated tablets was 6700440 tablets, and the estimated patient exposure to the marketed product worldwide was 4590 patient years.

The estimated patient exposure to the marketed product worldwide was 4,590 patient years. A total of 966 events were reported cumulatively from post-marketing data sources. Of these 966 events, 790

events (81.8%) were derived from spontaneous reports, including regulatory authority and literature. Of these 790 events, 161 events were serious (20.4%) and 629 events were non-serious (79.6%). The remaining 176 events (18.2%) were derived from non-interventional post-marketing studies and other solicited sources.

2.5.1. Discussion on clinical safety

The safety profile of darolutamide in combination with docetaxel in the intended indication mHSPC was mainly based on data from the pivotal study 17777 (DCO date: 25 Oct 2021) including 652 patients with mHSPC treated with darolutamide + docetaxel + ADT and standard ADT and 650 patients with mHSPC treated with placebo+ docetaxel and standard ADT. Supportive safety data were provided by the mCRPC pool including Phase 1/2 darolutamide studies in patients with mCRPC (n=173) and the non-cancer subject pool including Phase 1 single dose darolutamide studies (n=80).

In Study 17777, docetaxel was administered at a dose of 75 mg/m^2 as an IV infusion every 21 days for 6 cycles, starting within 6 weeks after the start of study drug, ADT (LHRH agonist/ antagonist concurrently or bilateral orchiectomy) was started ≤12 weeks before randomization and continued throughout the study and darolutamide and its matching placebo were administered at a dose of 600 mg BID.

Extent of exposure

The median treatment duration was longer in the darolutamide + docetaxel + ADT arm than the placebo + docetaxel + ADT arm, i.e. 41.0 months and 16.7 months, respectively. Difference between the 2 arms might be partly explained by the percentage of discontinuation of study treatment due to disease progression, i.e. 54.1% of treatment discontinuation in the darolutamide + docetaxel + ADT arm vs 80.4% in the placebo + docetaxel + ADT arm of the FAS. The average daily dose of study drug was comparable across the two treatments arms. The median percent of study drug planned dose was 100% and the mean was above 97% in both treatment arms, reflecting a good treatment compliance. The exposure to docetaxel was well balanced among the 2 treatment arms with 87.6% of subjects in the darolutamide + docetaxel + ADT arm and 85.5% in the placebo + docetaxel + ADT arm who received 6 cycles of docetaxel treatment. The average docetaxel cycle dose received was similar across the two treatment arms.

At the DCO there were 424 patients (32.5%) still on treatment, 299 (45.9%) receiving darolutamide and 125 (19.1%) receiving placebo. There were 105 (16.1%) patients in the darolutamide arm and 38 (5.8%) in the placebo arm that received treatment for >48 months.

The fact that patients remained significantly longer time in the darolutamide arm reflects that the tolerability of darolutamide was acceptable, unmanageable side effects did not occur frequently and these patients had not progressed.

Importantly, the addition of darolutamide did not translate into a lower number of docetaxel cycles administered: 87.6% of patients in the darolutamide arm received 6 cycles of docetaxel, in comparison with 85.5% patients in the placebo arm. In the context of a combination therapy with chemotherapy, this observation is reassuring. The number of dose modifications for the study drug was higher in the darolutamide arm than in the placebo arm (670 vs. 463), as expected. However, the proportion of patients with dose modifications was overall comparable between treatment arms. The percentage of events with TEAE as primary reason for study drug dose modification was 37.0% for darolutamide and 32.0% for placebo. No differences were observed between treatment arms in dose modification of docetaxel due to TEAEs (46.5% and 43.2%). There were more patients with ≥ 10 dose modifications per patient in the darolutamide arm than in the placebo arm (7.9% vs. 4.4%).

Overall, the patient exposure is considered to be sufficient to characterize the safety profile of darolutamide in combination with docetaxel in the proposed indication.

Adverse events

The overview of TEAEs is comparable across the treatment arms. Almost all the patients experienced a TEAE, i.e. 99.5% in the darolutamide + docetaxel + ADT arm and 98.9% in the placebo + docetaxel + ADT arm. Slightly more TEAEs leading to study drug dose modification were reported in darolutamide + docetaxel + ADT arm than placebo + docetaxel + ADT arm, i.e. 25.9% vs 17.2%, while the TEAEs leading to docetaxel dose modification were similar across the treatment arms, i.e. 32.8% and 32.9%. The majority of the TEAEs reported were severe with 70.2% of Grade ≥3 TEAEs in darolutamide + docetaxel + ADT arm and 67.5% in placebo + docetaxel + ADT arm, with a greater rate of docetaxel-related Grade ≥3 TEAEs (42.6% in both arms) compared to study drug-related Grade ≥3 TEAEs (9.5% in darolutamide + docetaxel + ADT arm and 6.3% in placebo + docetaxel + ADT arm).

The most commonly reported TEAEs were generally similar between the treatment arms. The most common events (≥25% of patients in either treatment arm) included alopecia, fatigue, anaemia, arthralgia, oedema peripheral, neutrophil count decreased, and diarrhoea. Those observed TEAEs were consistent with the known safety profile of docetaxel and darolutamide.

The most common TEAEs reported with ≥3 percentage points higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm were decreased appetite (18.6% vs 13.1%), hypertension (13.0% vs 9.1%), AST increased (14.0% vs 10.5%), and pain in extremity (15.0% vs 12.0%). When adjusted for the difference in study drug treatment duration, the EAIRs of these events were comparable between the treatment arms.

Overall, events with a worst grade of 3, 4, or 5 were reported with low incidences within the most common TEAEs, with the exception of the following Grade 3 or 4 TEAEs that occurred in ≥5% of patients in either treatment arm: neutrophil count decreased, febrile neutropenia, white blood count (WBC) count decreased, hypertension, anaemia and neutropenia.

Overall, these most common TEAEs occurred with similar incidences between the treatment arms, except for hypertension and ALT and AST increased, that occurred more frequently in darolutamide + docetaxel + ADT arm than placebo + docetaxel + ADT arm.

Concerning TEAEs over time, the incidence of commonly reported TEAEs, including alopecia, fatigue, anaemia, arthralgia, oedema peripheral, neutrophil count decreased, diarrhoea, WBC count decreased, neuropathy peripheral, and peripheral sensory neuropathy, were similar between the treatment arms. Prevalence followed a similar general decreasing trend for most of the TEAEs listed above. The trend of increasing prevalence of arthralgia, hypertension, and hyperglycaemia, observed in both treatment arms, could be explained due to the underlying comorbidities of the elderly patient population along with metastatic disease.

Adverse events of special topics

Among the TEAEs of special topic identified as potential or known risks associated with ADT or with anti-androgens, comparable incidence across the two treatment arms were observed except for the following events (by grouped TEAE term) reported at a higher rate in darolutamide + docetaxel + ADT arm than placebo + docetaxel + ADT arm: rash (16.6% vs 13.5%), diabetes (15.2% vs 14.3%), hypertension (13.8% vs 9.4%), bone fractures (7.5% vs 5.1%), fall (6.6% vs 4.6%), breast disorders (3.2% vs 1.5%) and mental impairment disorders (3.5% vs 2.3%). It is noted that the incidence of the TEAEs of special interest was greater in the study 17777 compared to the ARAMIS study that supported the approval of darolutamide in nmCRPC.

Since patients in the darolutamide arm remained significantly longer time on treatment than patients in the placebo arm, the incidences of AEs could be impacted by this difference. For this reason, the incidences adjusted by time and over time were provided. The results suggested that most AEs occurred within the first 6 months of treatment, and that afterwards the incidences decreased notably. It should be noted that "hypertension" did not seem to follow this pattern since it was less clear that incidences decreased over time. AEs prevalence also decreased over time with a similar trend among PTs.

Hypertension was newly identified as an ADR, with the grouped term hypertension (data-driven: PTs hypertension, blood pressure increased, hypertensive crisis, hypertensive emergency) reported at a higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (51.3% vs 49.2%). Hypertension was reported in 13.8% of patients treated with darolutamide+docetaxel and 9.4% of patients treated with placebo+docetaxel.Grade 3 hypertension was reported in 6.4% of patients treated with darolutamide+docetaxel compared to 3.5% of patients treated with placebo+docetaxel. One patient had grade 4 hypertension in each treatment arm. One case was reported as grade 5 hypertension with grade 5 arteriosclerosis in the darolutamide+docetaxel arm. This patient had a long standing history of hypertension and smoking and the case occurred more than 3 years after starting darolutamide treatment. Events of hypertension were reported more commonly in patients with no medical history of hypertension in both treatment arms.

The section 4.8 of the SmPC has been updated to include relevant information about cases of hypertension reported in mHSPC.

Overall, no major differences were observed between treatment arms regarding AEOSIs, but there was a higher incidence of breast disorders/gynaecomastia, which was double in the darolutamide arm compared with the placebo arm (3.2% vs 1.5%). All these events were of Grade 1/2. After adjusting for treatment exposure, the exposure-adjusted incidence rate (EAIR) remained higher in the darolutamide arm (1.2 vs 0.8). In Study 17712 (ARAMIS) the profile of events of breast disorders/gynaecomastia was similar: 2.3% vs. 1.6%, further suggesting that there might be an increased risk of occurrence of these events with darolutamide, which has been somehow replicated in Study 17777 (ARASENS). Considering the replication of results in two different studies, the double frequency reported between arms in Study 17777 (ARASENS), and the fact that gynaecomastia is a known ADR for another second-generation androgen receptor inhibitor (i.e. enzalutamide), it is considered that there is a reasonable likelihood of a potential causal link that justifies the inclusion of this AE in section 4.8 of the SmPC. Therefore, "gynaecomastia" has been included in section 4.8, with frequency "common".

Six (0.9%) patients in the darolutamide and only 1 (0.2%) in the placebo arm reported an event of cerebral and intracranial haemorrhage. After adjusting for treatment exposure differences appeared lower, but still higher in the darolutamide arm (0.3 vs 0.1 per 100 PY, respectively). A pooled analysis from ARASENS and ARAMIS studies including 1606 patients in the darolutamide arm and 1204 in the placebo arm showed cerebral and intracranial haemorrhage events of any-grade in 8 patients (0.5%) in the darolutamide arm vs. 3 patients (0.2%) in the placebo arm, being the RR 2.11 (95% CI: 0.61; 7.36). Although the evidence so far available does not clearly indicate a causal role for darolutamide, the fact that these events are of high-grade severity and that potentially they can lead to death or cause long-term damage is worrisome. Therefore, the MAH will continue to closely monitor these events in the PSURs.

Additional primary malignancies were reported in 25 patients (3.8%) in the darolutamide arm vs. 16 patients (2.5%) in the placebo arm. Besides, more SAEs and deaths due to secondary malignancies were reported in the darolutamide arm than in the placebo arm. Although the difference between arms observed in Study 17777 (ARASENS) is small, a carcinogenicity risk has been associated with other

drugs from the same pharmacological class, and the non-clinical studies performed with darolutamide could not rule out this carcinogenicity risk. Therefore, based on the evidence so far available, the causal relationship with darolutamide could not be excluded and further monitoring should be warranted. As such, "carcinogenicity potential" has been reclassified from "missing information" to "important potential risk" in the RMP.

An increased incidence for new symptomatic pathological fractures (6.6% vs 2.4%) and spinal cord compression (5.4% vs 2.7%) was observed in the SSE-FS and Time to SSE tables. It is recognized that the cumulative incidence might have been affected by the different median time on treatment between arms. In study 17777, there was a higher rate of TEAEs of bone fractures including pathological fractures in darolutamide+docetaxel arm than placebo+docetaxel arm (8.3% vs 5.5%, respectively) but when adjusted for the difference in study drug treatment duration, the EAIRs of bone fractures were similar between the treatment arms (2.8 vs. 2.7 per 100 PY). Nevertheless bone fracture is a known ADR of darolutamide (see SmPC section 4.8), there was an imbalance of TEAEs of bone fractures across the treatment arms and the effect of additional androgen depletion additive to ADT is likely to have increased negative effects on bone mineral density over time and likely increased the risk for fracture with longer duration of darolutamide+docetaxel+ADT above placebo+docetaxel+ADT. Therefore, bone fracture has been added to the list of ADRs reported in combination with docetaxel in the mHSPC patients in section 4.8 of the SmPC.

Adverse drug reactions

The list of ADRs as reflected in the SmPC was elaborated based on the identification of a causal relationship between a TEAE and darolutamide. As a result, ALT increased, hypertension and gynaecomastia were identified as new ADRs of darolutamide.

Less ADRs were identified for the combination of darolutamide+docetaxel in mHSPC compared to darolutamide alone for the treatment of nmCRPC while the safety profile is more unfavourable in mHSPC than in nmCRPC. Since darolutamide was administered in combination with docetaxel, adverse reactions from both darolutamide and docetaxel can be confounded and prevent the identification of a clear association between TEAE and one of the active substances.

Serious adverse events / deaths

In terms of death´s causes, overall there is no evidence of any trend, suggesting that the causes of death were similar in nature between arms. The only cause of death by PT reported with a higher incidence in the darolutamide arm than in the placebo arm was "COVID-19 pneumonia": 0.6% vs. 0.2%; although an additional death coded as "COVID-19" was also reported in the darolutamide arm. The clinical relevance of this observation is uncertain taking into account that the rate of infections was not higher in the darolutamide arm in comparison with the placebo arm, and considering the small number of events.

Special attention should be given to deaths related to cardiac and vascular disorders: in the darolutamide arm there were 7 deaths during treatment and within 30 days post permanent treatment discontinuation caused by cardiac and vascular disorders (PTs: "arteriosclerosis"+"hypertension"; "anaesthetic complication cardiac"; "cardiac failure acute"; "myocardial infarction"; "cardiac disorder"; "acute myocardial infarction"; "cardiac arrest"), and 2 additional deaths caused by "haemorrhagic stroke" and "subarachnoid haemorrhage". Of note, only 3 deaths related to cardiac and vascular disorders were reported in the placebo arm (2 due to "cardiac arrest" and 1 due to "cardiac failure"), together with an additional death caused by "cerebrovascular accident". Although none of the deaths of the darolutamide arm was considered as related by the investigator because patients had several underlying confounding factors. Further, in the darolutamide arm of study ARASENS there were 2

deaths due to a secondary malignancy in contrast to no reported deaths in the placebo arm. The 2 deaths were considered a second primary malignancy (urothelial cell carcinoma and gastric cancer, respectively) and unrelated to darolutamide. Subjects died 3 and 2 years after receiving the first dose of darolutamide, respectively.

SAE rates, although considerably high (probably impacted by the concomitant administration of docetaxel), were similar between treatment arms, i.e. 44.8% vs 42.3%, respectively. Febrile neutropenia was the most common SAE and was reported in 6.1% vs. 6.0% of patients in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively. Neutrophil count decreased was the only SAE that occurred in ≥1% of patients at a higher incidence in darolutamide + docetaxel + ADT arm compared to placebo + docetaxel + ADT arm (2.8% vs 1.5%). Overall, no SOC was particularly higher in the darolutamide arm in comparison with the placebo arm, except for "neoplasms benign, malignant and unspecified (including cysts and polyps)", which was reported in 4.1% in the darolutamide arm vs. 2.3% in the placebo arm and considered study drug related in 0.2% in darolutamide group (one case of myelofibrosis) and 0 in placebo group.

Laboratory findings

The most commonly reported (≥50% of patients in either arm) laboratory abnormalities (any grade) were anaemia, hyperglycaemia, ALP increased, lymphocyte count decreased, WBC decreased, and neutrophil count decreased. Hematotoxicity is characterized with the use of docetaxel and anaemia and neutropenia are known risk associated with docetaxel. The incidence of anaemia, lymphocyte count decreased and WBC decreased was similar across the two treatment arms. Laboratory abnormalities that were reported with ≥5 percentage points higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm included blood bilirubin increased (19.6% vs. 10.0% of patients, respectively), neutrophil count decreased (50.6% vs. 45.5%), and hyperkalaemia (26.0% vs. 20.5%).

"Neutrophil count decreased" was reported with a high incidence in both arms, but the incidence of G1-4 events and the incidence of G4 events were similar between arms: 50.6% vs. 45.5% and 22.1% vs. 19.4% respectively. Neutrophil count decreased is a known ADR of darolutamide and docetaxel. Therefore, it has been included in section 4.8 of the SmPC.

"AST/ALT increased" were reported with a high incidence, but the incidence of G1-4 events was quite similar between arms (around 40%). Furthermore the incidence of G4 events was low in both arms. Section 4.8 of the SmPC includes ALT/AST increased as ADRs.

With regards to blood bilirubin, it can be concluded that there is a causal role of darolutamide in combination with docetaxel in triggering the laboratory abnormality of blood bilirubin increased. These results are in line with the exposure-response analysis which showed that the change in total blood bilirubin over time in mHSPC patients was statistically different in the darolutamide + docetaxel + ADT than in the placebo + docetaxel + ADT arm. Therefore it has been included in section 4.8 of the SmPC.

Hepatotoxicity

Overall, the elevations of ALT, AST and blood bilirubin were more reported in patients treated with darolutamide + docetaxel + ADT than those treated with placebo+docetaxel, and liver functions increased were mostly of low grade of severity.

Cases of DILI were reported in Study 17777 and their occurrence was balanced across the 2 arms. However more serious cases were observed with darolutamide + docetaxel + ADT compared to

placebo+docetaxel. There were 2 possible Hy's Law cases in darolutamide + docetaxel + ADT arm and one case in placebo + docetaxel + ADT arm, and both cases were reversible.

In addition, the MAH provided in the document on signal evaluation for Drug-Induced Liver Injury (DILI) across all darolutamide clinical trials and 5 cases were considered to provide strong evidence for a causal association between darolutamide and idiosyncratic hepatocellular liver injury and both 5 were serious cases: 2 cases from ARASENS (Study 17777), 2 from ARAMIS (Study 17712), and 1 case that met Hy's Law from an investigator sponsored research study (ODENZA).

Section 4.8 of the SmPC has been updated to reflect the cases of hepatic transaminase elevations suggestive of a DILI related to darolutamide. In addition, a warning has been added in section 4.4 to reflect that in case of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to darolutamide, the treatment should be permanently discontinued.

Vital signs

Overall, no meaningful differences in the changes of mean or median values for blood pressure measurements, body weight, body mass index (BMI), and heart rate were observed across the two treatment arms.

Safety in special population

In both arms, the incidence of Grade 4-5 TEAEs, SAEs and TEAEs leading to docetaxel dose modification and permanent discontinuation increased with increasing age. While comparing the two treatment arms, the overview of TEAEs was comparable in the age groups <65 and 75-84 except for TEAEs leading to study drug dose modification and permanent discontinuation of study drug for these 2 age groups. An imbalance was however observed in the age group 65-74 that included the majority of the subjects in study 17777 (n=303 in darolutamide + docetaxel + ADT arm and n=305 in placebo + docetaxel + ADT arm) with a higher proportion of Grade 3-4 TEAEs, SAE and TEAEs leading to study drug dose modification and permanent discontinuation of study drug in darolutamide + docetaxel + ADT arm compared to the placebo + docetaxel + ADT arm.

In both treatment arms, the number of patients with moderately impaired renal function at baseline was smaller than the number of patients with mildly impaired or normal renal function. Comparable overview of TEAEs by renal function was observed across the treatment arms except TEAEs leading to study drug modification in mild RI that were more reported in darolutamide + docetaxel + ADT arm than placebo + docetaxel + ADT arm (30.5% vs 20.5%).

There were 2 patients in the darolutamide + docetaxel + ADT arm with moderately impaired hepatic function, and the number of patients with mildly impaired hepatic function was small in both treatment arms; therefore, comparisons across hepatic function groups should be made with caution. Overall, the incidences of any TEAEs, TESAEs, and TEAEs leading to permanent discontinuation or dose modification were generally similar between the hepatic function groups in both treatment arms.

Regarding subgroups by geographical region, it should be noted that Asian patients had an increased rate of TESAEs and grade 4 events in both arms in comparison with patients from other regions. Notably, an increase in the TEAEs leading to docetaxel dose modification and docetaxel permanent discontinuation was observed in both arms, suggesting that the worse toxicity profile observed in this subgroup of patients was driven by the docetaxel administration and not by the darolutamide administration. Specifically, by PT this increase seemed to be associated with an increase rate of "neutrophil count decreased", "white blood cell count decreased" and "anaemia". The incidence of these TEAES was higher in the first 6 months, and afterwards it decreased over time. Apart from this apparent link between a worse tolerability in Asian patients and the administration of docetaxel, it should be noted that patients in the Asian Pacific region presented at study entry with a more

advanced disease stage, which could also play a role in the worse tolerability observed in this subgroup of patients. Other PTs were also significantly increased in Asian patients, such as "malaise", which was reported in 21.3% and 24.0% in the darolutamide and placebo arm, respectively; whereas in the other subgroups it was reported with an incidence lower than 5% in either arm. The clinical relevance of this observation remains unknown, although it does not seem to have an important impact on the safety profile of darolutamide.

The MAH also presented subgroups analysis by concomitant statin use. Overall, no clinically meaningful differences were observed among subgroups, although the incidence of TESAEs and TEAEs leading to study drug or docetaxel dose modification were higher in the subgroup of patients taking statins concomitantly. However, this observation should be interpreted with caution due to the smaller size of the subgroup of patients taking statins (N=183) than the subgroup of patients not taking statins (N=480). The incidence of pre-defined TEAEs reflecting frequent undesirable effects of statins (ALT/AST/transaminases increased, muscular weakness, renal failure/impairment, etc) were also assessed in those subsets and the results did not show any significant imbalance which could be explained by drug-drug interactions between darolutamide and statins.

Discontinuation due to adverse events

Overall TEAEs leading to permanent discontinuation of study drug were more reported in darolutamide + docetaxel + ADT arm than placebo + docetaxel + ADT arm (13.5% vs 10.6%, respectively) while those leading to permanent docetaxel discontinuation occurred more frequently in the placebo + docetaxel + ADT arm than the darolutamide + docetaxel + ADT arm (10.3% vs 8.0%, respectively). All TEAEs leading to discontinuation of study drug and docetaxel occurred at low rate <1% except bone pain in placebo + docetaxel + ADT arm. The most common TEAEs leading to permanent discontinuation of study drug (in ≥5 patients in either treatment arm) were AST increased (0.9% vs. 0.3%), ALT increased (0.8% vs. 0.2%) and bone pain (0.3% vs. 1.4%).

Regarding the incidence of TEAEs leading to interruption of the study drug, it should be highlighted that the incidence was markedly higher in the darolutamide arm (22.9%) vs. the placebo arm (15.7%), mainly due to Grade 3 TEAEs. The higher rate of interruptions seems to be driven mainly by the imbalance in some PTs, such as "ALT and AST increased", as well as "febrile neutropenia"; which were reported with approximately double frequency in the darolutamide compared with the placebo arm. TEAEs leading to interruption of docetaxel were reported with a similar incidence in both arms. The incidence of TEAEs leading to dose reduction of the study drug was overall low, although in the darolutamide arm it was twice as high as the incidence in the placebo arm (8.7% vs 4.3%), also apparently driven mainly by "ALT and AST increased" PTs. The incidence of TEAEs leading to docetaxel dose reduction was similar between arms, suggesting that darolutamide addition did not have a detrimental effect on the planned administration of docetaxel.

Post marketing experience

No new safety concerns were identified from darolutamide post-marketing surveillance.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of darolutamide + docetaxel + ADT in mHSPC was comparable to placebo+docetaxel but worsened compared to the known safety profile of darolutamide in nmCRPC with a toxicity mainly driven by the combination with docetaxel. The majority of the reported adverse events were severe (Grade ≥3) in both treatment arms, with 70.2% of Grade ≥3 TEAEs in darolutamide + docetaxel + ADT arm and 67.5% in placebo + docetaxel + ADT arm. The incidence of

serious adverse events was comparable across the treatment arms but greater in study 17777 (ARASENS) than in ARAMIS study in mCRPC patients for both treatment groups. Hypertension, ALT increased and gynaecomastia were newly identified as ADRs of darolutamide. Hepatotoxicity arised from the safety data of clinical trials in which 5 cases were considered to provide strong evidence for a causal association between darolutamide and idiosyncratic hepatocellular liver injury. In both cases the hepatotoxicity events were manageable. Concerning the carcinogenicity risk, which has been previously associated with other drugs from the same pharmacological class, based on the available evidence presented so far, the causal relationship with darolutamide could not be excluded. Therefore, "carcinogenicity potential" has been reclassified from "missing information" to "important potential risk" in the RMP and additional pharmacovigilance activities have been proposed to further assess this risk.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Table 78: Summary of safety concerns

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

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

Pharmacovigilance plan

Table 79: 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				
None				

Risk minimisation measures

Table 80: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

Table 80: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	
Cardiovascular events in patients with significant CV history	**Routine risk communication** SmPC section 5.1 Pharmacodynamic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Updates on important potential risks will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Follow-up questionnaire on cardiac disorders.
Carcinogenicity potential	**Routine risk communication** SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk** None proposed **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Updates will be provided in each PBRER/PSUR, if new safety relevant information is received during the period of the report. Follow-up questionnaire on second primary malignancies

Table 80: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 ,5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all changes to the Product Information.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to NUBEQA 300 mg film-coated tablets package leaflet. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application was to extend the indication of Nubeqa (darolutamide) to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

The recommended indication is: NUBEQA is indicated for the treatment of adult men with metastatic hormone sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy.

3.1.2. Available therapies and unmet medical need

Metastatic HSPC, also known as metastatic castration-sensitive prostate cancer (mCSPC), is defined as metastatic prostate cancer in patients who have not yet received or are continuing to respond to anti-hormonal therapy. Depriving prostate cancer cells of androgen is the primary form of therapy since prostate cancer depends on androgen for growth and survival. ADT is defined as surgical castration by bilateral orchiectomy or medical castration with LHRH agonist/antagonists.

Although almost all men with mHSPC initially respond to ADT, most will progress to mCRPC within 1 to 3 years of their initial diagnosis.

According to ESMO guideline on cancer of the prostate (2020), the recommended treatment of hormone naïve setting is ADT (luteinizing hormone-releasing hormone [LHRH] agonist or surgical castration) in combination with one of the following approved treatments of mHSPC: abiraterone, a CYP17 inhibitor (with prednisone or prednisolone), an ARI (apalutamide or enzalutamide), docetaxel with or without prednisone or prednisolone.

3.1.3. Main clinical studies

The pivotal study for this application is trial ARASENS (study 17777): a Phase III, multinational, randomized (1:1), double-blind, placebo-controlled study evaluating darolutamide 600 mg BID orally in combination with 6 cycles of docetaxel. Patients were randomised in a 1:1 ratio to receive either darolutamide or placebo, each combined with docetaxel and ADT.

The primary endpoint was OS. The secondary endpoints were the time to castration-resistant prostate cancer (CRPC), the time to pain progression, symptomatic skeletal event-free survival (SSE-FS), the time to first symptomatic skeletal event (SSE), the time to initiation of subsequent systemic antineoplastic therapy, the time to worsening of disease-related physical symptoms, the time to initiation of opioid use for ≥7 consecutive days.

3.1.4. Favourable effects

The primary endpoint of the pivotal study was met, with a statistically significant improvement of OS in the darolutamide + docetaxel + ADT arm compared to placebo + docetaxel. ARASENS study showed a reduction of the risk of death of 32.5% in the darolutamide + docetaxel + ADT arm compared to the

placebo + docetaxel + ADT arm (HR: 0.675; 95% CI: [0.568; 0.801]), and the log-rank test was statistically significant with a one-sided p<0.0001.

The start of a new systemic antineoplastic therapy was reported for 33.6% of patients in the darolutamide + docetaxel + ADT arm compared with 60.4% in the placebo + docetaxel + ADT arm which represents a statistically significant and clinically meaningful improvement with an HR of 0.388, 95% (CI: [0.328; 0.458]; p<0.0001.

CRPC was documented for 225 (34.6%) patients in the darolutamide + docetaxel + ADT arm and 391 (59.8%) patients in the placebo + docetaxel + ADT arm. A statistically significant prolonged time to CRPC was observed for patients in the darolutamide + docetaxel + ADT arm compared with the placebo + docetaxel + ADT arm, with an HR of 0.357 (95% CI: [0.302; 0.421]); p<0.0001.

SSEs were reported in 14.6% of patients in the darolutamide + docetaxel + ADT arm compared with 16.5% in the placebo + docetaxel + ADT arm with a numerical improvement (ie, a delay) of time to first SSE for patients in the darolutamide + docetaxel + ADT arm, with an HR of 0.712 (95% CI: [0.539; 0.940]); p=0.0081. The median time to first SSE was not reached (95% CI: [A; A]) in either treatment arm. The majority of the first SSEs were External beam radiation therapy to relieve skeletal symptoms, reported for 63.2% of patients with an SSE in the darolutamide + docetaxel + ADT arm and 82.4% of patients with an SSE in the placebo + docetaxel + ADT arm.

Findings from secondary efficacy analyses all showed statistically significant results in favour of darolutamide + docetaxel + ADT arm except for the Time to worsening of disease-related physical symptoms based on the NCCN–FACT-FPSI-17 questionnaire.

3.2. Uncertainties and limitations about favourable effects

A relatively large proportion of patients had premature emergency unblinding performed at the study site by the investigator to inform the choice of subsequent therapy. The premature unblinding was limited to the investigator and patient, and study team members remained blinded to treatment allocation until the formal study unblinding at the time of analyses. The impact and potential bias induced by premature unblinding on subsequent patient measurements were discussed and post-hoc analyses were provided for the endpoints that were considered to be most likely influenced by premature unblinding: time to pain progression and time to worsening of physical disease-related symptoms. Although bias cannot be completely ruled out in the presence of premature unblinding, the additional information and post-hoc analyses performed by the MAH provided some reassurance that the study conclusions were not affected.

3.3. Unfavourable effects

The majority of the patients in study 17777 experienced a TEAE, and the TEAEs observed were mostly severe (Grade ≥3) in both treatment arms. The incidence of TEAEs, Grade 1-2 TEAEs and Grade 3-4 TEAEs was comparable between the darolutamide + docetaxel + ADT and the placebo + docetaxel + ADT arms in study 177777. The majority of the TEAEs reported were severe with 70.2% of Grade ≥3 TEAEs in darolutamide + docetaxel + ADT arm and 67.5% in placebo + docetaxel + ADT arm. The most common events (≥25% of patients in either treatment arm) included alopecia, fatigue, anaemia, arthralgia, oedema peripheral, neutrophil count decreased and diarrhoea. The most common TEAEs reported with ≥3 percentage points higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm were decreased appetite, hypertension, AST increased and pain in extremity.

The SAEs were reported at comparable rates in darolutamide + docetaxel + ADT and placebo + docetaxel + ADT arms, i.e. 44.8% vs 42.3%, respectively. Febrile neutropenia was the most common SAE across the two treatment arms and neutrophil count decreased was the only SAE that occurred in ≥1% of patients at a higher incidence in darolutamide + docetaxel + ADT arm compared to placebo + docetaxel + ADT arm (2.8% vs 1.5%). The Grade 5 TEAEs were reported at similar rate across the treatment arms (4.1% and 4.0% in the darolutamide + docetaxel + ADT arm and the placebo + docetaxel + ADT arm, respectively).

Hypertension and ALT increased were newly identified as ADRs

The grouped term hypertension (data-driven: PTs hypertension, blood pressure increased, hypertensive crisis, hypertensive emergency) was reported at a higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (51.3% vs 49.2%). Also Grade 3 hypertension was higher in darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm (6.4% vs 3.5% of patients, respectively). One case of Grade 5 Atherosclerotic Cardiovascular Disease and Hypertensive was reported in darolutamide + docetaxel + ADT arm.

ALT increased was reported with a slightly higher incidence in the darolutamide + docetaxel + ADT arm than in the placebo + docetaxel + ADT arm. In addition, an increased frequency of AST elevations and blood bilirubin increased, already identified as adverse drug reactions of darolutamide in nmCRPC patients, were observed in patients treated with darolutamide in combination with docetaxel in comparison with patients who received placebo in combination with docetaxel.

Hepatotoxicity cases were reported in ARASENS study. Cases of DILI were reported in Study 17777 and their occurrence was balanced across the 2 arms. In addition, the MAH provided a document on signal evaluation for DILI across all darolutamide clinical trials and 5 cases were considered to provide strong evidence for a causal association between darolutamide and idiosyncratic hepatocellular liver injury and both 5 were serious cases: 2 cases from ARASENS (Study 17777), 2 from ARAMIS (Study 17712), and 1 case that met Hy's Law from an investigator sponsored research study (ODENZA).

Therefore, section 4.8 of the SmPC has been updated to reflect the cases of hepatic transaminase elevations suggestive of a DILI related to darolutamide. In addition, a warning has been added in section 4.4 to reflect that in case of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to darolutamide, the treatment should be permanently discontinued.

3.4. Uncertainties and limitations about unfavourable effects

The characterization of the safety profile of darolutamide in mHSPC based on data from study 17777 remains challenging due to the combination with docetaxel. Reported adverse reactions incidences may not be attributable to darolutamide alone but may contain contributions from other medicinal products used in combination. This has been reflected in section 4.8 of the SmPC in where the adverse reactions observed in patients with mHSPC treated with darolutamide in combination with docetaxel have been listed (see Section 4.8, Table 2 of the SmPC). Additional safety information when darolutamide is administered in combination can be found in the product information of the individual medicinal products

Despite numbers were low, a higher incidence of cerebral and intracranial haemorrhage was reported in the darolutamide arm compared with the placebo arm. While confounding factors were present a potential relationship with darolutamide (+docetaxel) could not be ruled out at this stage and will be further monitored in the PSURs.

With regards to the carcinogenicity risk, a causal association with darolutamide couldn't be ruled out based on the available evidence presented so far. As a result, "carcinogenicity potential" has been

reclassified from "missing information" to "important potential risk" in the RMP and two additional pharmacovigilance activities have been proposed to further assess this risk.

3.5. Effects Table

Table 81: Effects Table for Darolutamide in combination with docetaxel for the treatment of mHSPC (data cut-off: 25 Oct 2021)

Effect	Short description	Unit	Darolutamide + docetaxel + ADT (N=651)	Placebo + docetaxel + ADT (N=654)	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Overall Survival	N (%)	229 (35.2%)	304 (46.5%)		Study 17777 (ARASENS)
		HR[a]	0.675; CI 95% (0.568; 0.801) p<0.0001			
Unfavourable Effects						
Grade ≥3 TEAEs		%	70.2	67.5	The toxicity is likely driven by the combination with docetaxel	Study 17777 (ARASENS)
SAEs		%	44.8	42.3		
Hypertension	Including PTs hypertension, blood pressure increased, hypertensive crisis, hypertensive emergency	%	13.0	9.1	Grade 3 hypertension highly reported in darolutamide + docetaxel + ADTarm than in the placebo + docetaxel + ADT arm, one Grade 5 event in darolutamide + docetaxel + ADT arm.	
ALT increased	TEAE frequency	%	15.6	12.9	TEAEs of Grade 3/4 ALT increased occurred more frequently in the darolutamide + docetaxel + ADT arm compared to the placebo + docetaxel + ADT arm	
	Grade 3/4 ALT increased	%	2.8	1.7		

Abbreviations: ALT: Alanine liver transaminases, PTs: Preferred terms, SAEs: serious adverse events, TEAEs: treatment-emerging adverse event; a: Hazard ratio < 1 favours darolutamide

The following secondary efficacy endpoints showed a statistically significant advantage in favour of the patients in the darolutamide+docetaxel arm compared to patients in the placebo+docetaxel arm: time to castration-resistant prostate cancer (median NR vs 19.1 months; HR=0.357, p<0.0001); time to first symptomatic skeletal event (median NR vs NR months; HR=0.712, p=0.0081); time to initiation of subsequent antineoplastic chemotherapy (median NR vs 25.3 months; HR=0.388, p<0.0001); time to pain progression (median NR vs 27.5 months; HR=0.792, p=0.0058); symptomatic skeletal event free survival time (median 51.2 vs 39.7 months; HR=0.609, p<0.0001).

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Darolutamide + docetaxel as add-on therapy to standard ADT showed a clinically relevant improvement in terms of OS and a delay in the onset of mCRPC. These results were consistently supported by most secondary endpoints which are considered to indirectly reflect the quality of life of patients. The combination darolutamide + docetaxel + ADT in the ARASENS study, significantly reduced the onset of castration-resistant disease, prolonged the time to the first SSE, and the time to subsequent systemic antineoplastic therapy.

The overall safety profile of darolutamide in the treatment of adult men with metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) and docetaxel was consistent with the known safety profile of darolutamide and there were no unexpected findings. The majority of adverse events reported with darolutamide + docetaxel + ADT combination in mHSPC patients were severe and the frequency of serious adverse events was not negligible but comparable to the one reported with placebo+docetaxel+ADT. Although the combination with docetaxel makes the characterization of the safety profile of darolutamide in mHSPC challenging, ALT increased, hypertension and gynaecomastia were identified as new ADR of darolutamide. Furthermore, cases of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to darolutamide were reported with darolutamide and managed with darolutamide discontinuation. Overall, the safety profile is considered manageable and well tolerated, based on the frequencies of SAEs, AE leading to treatment discontinuation and AES leading to death, with no major differences over placebo.

3.6.2. Balance of benefits and risks

In study ARASENS darolutamide + docetaxel + ADR showed a clinically relevant and statistically significant benefit in terms of OS versus docetaxel + ADT for patients with mHSPC while the safety profile of darolutamide with docetaxel was consistent with the known safety profile of the two products and manageable with adequate risk minimisation measures.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

The overall B/R of Nubeqa is positive in the following indication:

NUBEQA is indicated for the treatment of adult men with metastatic hormone sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy (see section 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the

following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy, based on final results from Study 17777 (ARASENS); this is a randomized, double-blind, placebo-controlled Phase 3 study designed to demonstrate the superiority of darolutamide in combination with docetaxel over placebo in combination with docetaxel in OS in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

The request for one year of market protection for a new indication was withdrawn by the MAH during the current procedure.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

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

Risk management plan (RMP)

The Marketing authorisation holder (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.

In addition, 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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/004790/II/0009'.