Amsterdam, 19 June2025
EMA/CHMP/141078/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nubeqa

International non-proprietary name: Darolutamide

Procedure No. EMEA/H/C/004790/II/0024

Note

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

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List of abbreviations

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
AFU	Association Française d'Urologie
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ARi	Androgen receptor inhibitor
ARPi	Androgen receptor pathway inhibitor
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BID	Twice daily
BPI-SF	Brief Pain Inventory – Short Form
CCDS	Company core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
EAIR	Exposure-adjusted incidence rate
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EHR	Electronic health records
EMA	European Medicines Agency (EU)
ESMO	European Society for Medical Oncology
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLOBOCAN	Global Cancer Observatory
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILD	Interstitital lung disease
IWRS	Interactive web response system
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
mHSPC	Metastatic hormone-sensitive prostate cancer
NCCN	National Comprehensive Cancer Network
nmCRPC	Non-metastatic castration-resistant prostate cancer
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PFS2	Progression-free survival 2
PRO	Patient-reported outcomes
PS	Performance status

PSA	Prostate-specific antigen
PT	Preferred term
PV	Pharmacovigilance
PY	Participant year
QoL	Quality of life
QTcB	Corrected QT (Bazett's formulae)
QTcF	Corrected QT (Fridericia's formulae)
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	Roll-over study
ROW	Rest of the world
rPFS	Radiological progression-free survival
RWE	Real-world evidence
SA	Scientific advice
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SMQ	Standardized MedDRA query
SOC	System organ class
SSE	Symptomatic skeletal event
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UK	United Kingdom
ULN	Upper limit of normal
US	United States

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 14 October 2024 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 in combination with androgen deprivation therapy (ADT) the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for NUBEQA, based on final results from study 21140 (ARANOTE); this is a randomized, double-blind, placebo-controlled Phase 3 study of darolutamide to demonstrate the superiority of darolutamide in addition to ADT over placebo plus ADT in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and update the Package Leaflet to more patient friendly wording based on patient council feedback.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision 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.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 17 September 2020 (EMEA/H/SA/2639/3/2020/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	14 October 2024
Start of procedure:	2 November 2024
CHMP Rapporteur Assessment Report	23 December 2024
PRAC Rapporteur Assessment Report	7 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	23 April 2025
PRAC Rapporteur Assessment Report	24 April 2025
PRAC Outcome	08 May 2025
CHMP members comments	12 May 2025
Updated CHMP Rapporteur Assessment Report	16 May 2025
Request for supplementary information (RSI)	22 May 2025
CHMP Rapporteur Assessment Report	04 June 2025
PRAC Rapporteur Assessment Report	04 June 2025
PRAC members comments	10 June 2025
CHMP members comments	10 June 2025
Updated CHMP Rapporteur Assessment Report	13 June 2025
Updated PRAC Rapporteur Assessment Report	13 June 2025
CHMP Opinion	19 June 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Metastatic hormone-sensitive prostate cancer (HSPC), also known as metastatic castration-sensitive prostate cancer (mCSPC), is defined as metastatic disease in patients who have not yet received or are continuing to respond to antihormonal therapy. 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 presents with metastatic disease.

State the claimed therapeutic indication

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

Epidemiology and risk factors, screening tools/prevention

Prostate cancer is the second most frequently diagnosed cancer in men and the fifth leading cause of death due to cancer in the world. Based on GLOBOCAN 2024 estimates, 1.47 million new cases of prostate cancer were reported worldwide, with a higher prevalence in developed countries (Ferlay et al. 2024). In the US, the American Cancer Society predicted 299,010 new diagnoses and estimated 35,250 deaths from prostate cancer in 2024 (Siegel et al. 2024). In Europe, the estimated number of new prostate cancer cases in 2022 was 473,011, and the number of deaths was 115,182 (Ferlay et al. 2024).

Clinical presentation, diagnosis and stage/prognosis

Based on European country-specific registries, between 5.2% and 17.8% of newly diagnosed prostate cancers are metastatic (Hagel et al. 2009, Spandonaro et al. 2021).

Depriving prostate cancer cells of androgen is the primary form of therapy, since prostate cancer depends on androgen for growth and survival. Androgen deprivation can be achieved either surgically by orchiectomy or medically, by luteinising hormone-releasing hormone (LHRH) agonist/antagonists. Androgen deprivation therapy (ADT) remains the mainstay of the treatment of mHSPC and although the treatment landscape has rapidly evolved over the last few years, ADT alone is still widely prescribed in clinical practice. Although almost all patients with mHSPC initially respond to treatment, most will progress to metastatic castration-resistant prostate cancer (mCRPC) within a few years of their diagnosis. Progression to mCRPC has a significant, detrimental impact on the patient's prognosis, leading to increased mortality (Wenzel et al. 2021). Therefore, avoiding rapid progression to mCRPC is an important treatment goal for patients with mHSPC to maintain their quality of life (QoL) for as long as possible.

Management

Treatment landscape

The currently approved systemic treatment options for patients with mHSPC are summarised in Table 1.

Table 1 Approved systemic treatments for mHSPC

Approved systemic treatments for mHSPC

Product(s) name	MoA	Relevant indication	Approval year for mHSPC	Dose	Efficacy	Important safety and tolerability issues
ADT	GnRH agonist/antagonist	Prostate cancer		Depending on the molecule		Fatigue/asthenic conditions, bone fractures, fall, vasodilatation and flushing, breast disorders/gynecomastia, hypertension, cardiac disorders, diabetes mellitus and hyperglycemia, mental impairment disorders, depressed mood disorders, cerebrovascular disorders, and weight decreased[a]

Approved systemic treatments for mHSPC

Product(s) name	MoA	Relevant indication	Approval year for mHSPC	Dose	Efficacy	Important safety and tolerability issues
Darolutamide (NUBEQA) **+** **Docetaxel** NUBEQA USPI, 2023 Nubeqa EU SmPC, 2023	2nd generation ARi + Microtubule assembly inhibitor	mHSPC	2022 (US) 2023 (EU)	600 mg BID with food, equal to a daily dose of 1200 mg + 75 mg/m^2 docetaxel IV every 21 days for 6 cycles Concurrently with ADT	**ARASENS (N=1305)** • OS: HR=0.68 95% CI: [0.57; 0.80]	**USPI** **Warnings and precautions**: Ischemic heart disease, seizure, embryo-fetal toxicity **EU SmPC** **Special warnings and precautions for use:** CV disease, hepatic transaminase elevations
Enzalutamide (XTANDI) XTANDI USPI, 2023 Xtandi EU SmPC, 2024	2nd generation ARi	mHSPC	2019 (US) 2021 (EU)	160 mg p.o. QD Concurrently with ADT	**ARCHES (N=1150)** • rPFS: HR=0.39 95% CI: [0.30; 0.50] • Final OS: HR=0.66 95% CI: [0.53; 0.81]	**USPI** **Warnings and precautions:** Seizure, posterior reversible encephalopathy syndrome, hypersensitivity, ischemic heart disease, falls and fractures, embryo-fetal toxicity **EU SmPC** **Special warnings and precautions for use:** Seizure, posterior reversible encephalopathy syndrome, second primary malignancies, CV disease, hypersensitivity reactions

Approved systemic treatments for mHSPC

Product(s) name	MoA	Relevant indication	Approval year for mHSPC	Dose	Efficacy	Important safety and tolerability issues
Apalutamide (ERLEADA) ERLEADA USPI, 2023 Erleada EU SmPC, 2023	2nd generation ARi	mHSPC	2019 (US) 2020 (EU)	240 mg p.o. QD Concurrently with ADT	**TITAN (N=1052)** • rPFS: HR=0.48 95% CI: [0.39; 0.60] • Interim OS: HR=0.67 95% CI: [0.51; 0.89] • Final OS: HR=0.65 95% CI: [0.53; 0.79]	**USPI** **Warnings and precautions:** Cerebrovascular and ischemic CV events; fractures; falls; seizures; severe cutaneous adverse reactions, including Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic syndrome; embryo-fetal toxicity **EU SmPC** **Special warnings and precautions for use:** Seizure, falls and fractures, ischemic heart disease and ischemic cerebrovascular disorders, severe cutaneous adverse reactions (including drug reaction with eosinophilia and systemic symptoms and Stevens-Johnson syndrome/toxic epidermal necrolysis), interstitial lung disease
Abiraterone acetate (ZYTIGA) ZYTIGA USPI, 2021 Zytiga EU SmPC, 2022	Androgen biosynthesis inhibitor (CYP17 inhibitor)	High risk mHSPC	2018 (US) 2017 (EU)	1000 mg p.o. QD with 5 mg prednisone p.o. QD Concurrently with ADT	**LATITUDE (N=1199)** • rPFS[b]: HR=0.466 95% CI: [0.394; 0.550] • Interim OS: HR=0.62 95% CI: [0.51; 0.76] • Final OS: HR=0.66 95% CI: [0.56; 0.78]	**USPI** **Warnings and precautions:** Mineralocorticoid excess, adrenocortical insufficiency, hepatotoxicity, increased fractures and mortality in combination with radium Ra 223 dichloride, embryo-fetal toxicity, hypoglycemia **EU SmPC** **Special warnings and precautions for use:** Hypertension, hypokalemia, fluid retention and cardiac failure due to mineralocorticoid excess, hepatotoxicity and hepatic impairment, adrenocortical insufficiency, mineralocorticoid excess, decreased bone density, hyperglycaemia, hypoglycemia, skeletal muscle effects, increased fractures and mortality in combination with radium Ra 223 dichloride

Approved systemic treatments for mHSPC

Product(s) name	MoA	Relevant indication	Approval year for mHSPC	Dose	Efficacy	Important safety and tolerability issues
Docetaxel (TAXOTERE) Taxotere EU SmPC, 2023	Microtubule assembly inhibitor	mHSPC	NA (US)[c] 2019 (EU)	75 mg/m^2 IV 3-weekly for 6 cycles Concurrently with ADT	**STAMPEDE (N=1776)** • OS HR=0.76 95% CI: [0.62; 0.92] **CHAARTED (N=790)** OS HR=0.61 95% CI: [0.47; 0.80]	**EU SmPC** **Special warnings and precautions:** Neutropenia, GI reactions, hypersensitivity reactions, cutaneous reactions, fluid retention, respiratory disorders, severe peripheral neurotoxicity, cardiac toxicity, eye disorders, second primary malignancies, tumor lysis syndrome.

ADT=Androgen deprivation therapy; AE=Adverse event; ALT=Alanine aminotransferase; ARi=Androgen receptor inhibitor; AST=Aspartate aminotransferase; BID=Twice daily; CI=Confidence interval; CV=Cardiovascular; CYP=Cytochrome P450; EU=European Union; EU SmPC=European Union Summary of Product Characteristics; FDA=Food and Drug Administration (US); GI=Gastrointestinal; GnRH=Gonadotropin-releasing hormone; HR=Hazard ratio; IV=Intravenous; mCRPC=Metastatic castration-resistant prostate cancermHSPC=Metastatic hormone-sensitive prostate cancer; MoA=Mechanism of action; N=Number of patients; NA=Not applicable; OS=Overall survival; p.o.=Orally; QD=Once a day; rPFS=Radiological progression-free survival; US=United States; USPI=United States Prescribing Information

a. Source: (Michaelson et al. 2008, Rhee et al. 2015, Sharifi et al. 2005)
b. Included in Zytiga EU SmPC only.
c. Docetaxel is marketed and approved for mCRPC indication in the US.

Sources: USPIs: (ERLEADA® USPI 2023, NUBEQA® USPI 2023, XTANDI® USPI 2023, ZYTIGA® USPI 2021)

EU SmPCs: (Erleada SmPC 2024, Nubeqa SmPC 2023, Taxotere SmPC 2023, Xtandi SmPC 2024, Zytiga SmPC 2022)

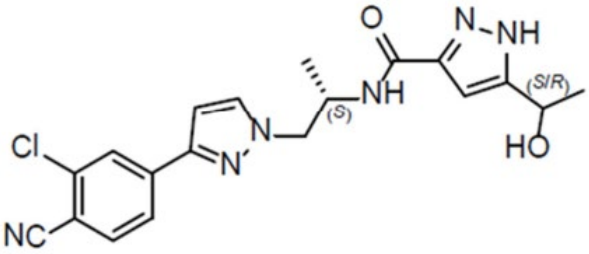
Although ADT is recognised as a standard of care for the treatment of mHSPC (NCCN 2025, ESMO 2023), ADT in monotherapy is discouraged unless there are clear contraindications to combination therapy (NCCN 2025). ADT with treatment intensification could be also a form of treatment optimisation and is strongly recommended for patients with mHSPC. Treatment intensification options include doublet therapy of ADT with abiraterone, apalutamide, or enzalutamide (all category 1); triplet therapy of ADT with docetaxel and abiraterone or darolutamide (categories 1) (NCCN2025).

Recent publications have shown that multiple determinants are associated with lack of treatment intensification, e.g. patient- and disease-related characteristics such as older age, comorbidities, and performance status (Dodkins et al. 2024, Raval et al. 2024a). For this patients population the ADT in monotherapy is still considered a valid option.

2.1.2. About the product

Darolutamide is a structurally distinct non-steroidal androgen receptor inhibitor (ARI) that binds with a high affinity and selectivity to the androgen receptor (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 (EMEA/H/C/004790/0000) for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. A second indication was approved in February 2023 for metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy (EMEA/H/C/004790/II/0009).

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.

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

Overview of clinical development program

As of 07 JUN 2024, darolutamide has been studied in 14 company-sponsored Phase 1 to Phase 3 clinical studies that are either completed or have reached primary completion, in which 2424 participants with prostate cancer have been treated with darolutamide.
The pivotal study to support efficacy and safety of darolutamide for the treatment in the mHSPC in this application is the pivotal Phase 3 ARANOTE study, an ongoing, randomized, double-blind, placebo-controlled study in patients with mHSPC. Safety profile is further supported by a pooled analysis of the ARANOTE and Phase 3 ARAMIS (in nmCRPC) safety results. Supportive results for the long-term safety of darolutamide are provided by Study 20321 (ROS).
The clinical studies presented in this application were or are being conducted in accordance with the ICH GCP, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed.

The MAH received Scientific Advice from the CHMP and the key outcomes of the CHMP Scientific Advice (EMEA/H/SA/2639/3/2020/II) are summarized in Table 2.

Table 2 Key regulatory milestones – EU

Regulatory milestone	Date	Key outcome
CHMP Scientific Advice (written feedback)	17 SEP 2020	Agreement on the proposed design of the pivotal Phase 3 clinical Study 21140 (ARANOTE): rPFS as primary endpoint supported by the key secondary endpoint OS Additional proposed secondary endpoints Statistical approach, including stratification factors, statistical assumptions, and efficacy analyses

CHMP=Committee for Medicinal Products for Human Use; EU=European Union; OS=Overall survival; rPFS=Radiological progression-free survival

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

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An update of the ERA has been carried out taking into account the latest ERA guidelines for medicinal products for human use adopted by the European Medicines Agency (EMA) on 15 February 2024, with entry into force on 1 September 2024 (EMEA/CHMP/SWP/4447/00 Rev. 1).

ERA studies conducted are summarized in the table below.

Table 3 *: Summary of main study results: Phase I*

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	OECD 301	Not degraded on day 29	Potentially P/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 $_{surfacewater}$	0.412	µg/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 7)			
Dissociation constant	OECD 112	Neutral			
Hydrolysis	OECD 111	Stable at pH 4, 7, and 9			
Vapour Pressure	OECD 104	2.61 x 10^{-5} Pa (20ºC)			
Ready Biodegradability Test	OECD 301	Not degraded on day 29			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Not required			Not required
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	128.29	mg/kg	Sediment dry weight, 10% Corg

2.2.2. Discussion on non-clinical aspects

An updated Environmental Risk Assessment (ERA) for darolutamide has been performed in accordance with the revised EMA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1, 2024). The refined PEC_{SW} was calculated as 0.412 µg/L. As this value exceeds the Phase I action threshold of 0.01 µg/L, a Phase II assessment was required.

In Phase II, the aquatic risk characterisation showed a NOEC of 28 µg/L, resulting in a $PNEC_{SW}$ < 2.8 µg/L and a risk quotient (RQ_{SW}) of 0.147, indicating no risk to the surface water compartment. The predicted environmental concentration in sediment ($PEC_{SED,DW}$) was calculated as 0.0788 mg/kgdw, compared to a $PNEC_{SED}$ of 1.28 mg/kgdw, resulting in an RQ_{SED} of 0.0614, also indicating no concern. For sewage treatment plants, PEC_{STP} was 4.12 µg/L and the $PNEC_{STP}$ was 1,290 µg/L, resulting in an RQ_{STP} of 0.0032, well below the level of concern. The groundwater PEC, estimated via bank filtration, was 0.103 µg/L, and the $PNEC_{Gw}$ was 0.28 µg/L, leading to an RQ_{GW} of 0.368.

Darolutamide is not readily biodegradable and shows persistence in sediment, with DT_{50} values of up to 252 days. The primary transformation product M-1, present at >10%, is very persistent, with DT_{50} values exceeding 2,100 days. However, the compound exhibits low bioaccumulation potential (log K_{ow} = 2.41) and does not demonstrate significant chronic aquatic toxicity.

Soil assessment shows the API value (452 L kg^{-1}) is below the trigger (<1,000 L kg^{-1}), so no soil risk assessment is needed. Secondary poisoning assessment is not needed (log KOW < 3).

In application of the new guideline (EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.), and in view of darolutamide's mechanism of action, it was necessary to investigate the potential disruptive endocrine effect of the concentrations released into the environment, mainly through a full life cycle study. As part of phase II tier A, short- and long-term studies were carried out in fish, fish short term reproduction and fish full life cycle test. The short-term study revealed no effect, while the full life study revealed a NOEC of 28 µg/L. The surface water assessment showed no risk (RQ =0.147).

2.2.3. Conclusion on the non-clinical aspects

In conclusion, darolutamide is not considered PBT or vPvB and poses no significant risk to the environment.

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

Table 4 Tabular overview of clinical studies in support of the current indication

Clinical phase	Bayer study no / Study name (Orion study no)	Countries/regions	Study period	Study design	Primary and secondary objectives	Study population	Treated participants/ Exposed participants	Treatment and dose	Location / Report no
Phase 3	21140 ARANOTE	Australia, Brazil, Canada, Chile, China, India, Latvia, Lithuania, New Zealand, Peru, Russia, South Africa, Spain, Taiwan, and Ukraine	FPFV 23FEB2021 Primary completion: 07JUN2024	Randomized (2:1), double-blind, placebo controlled	Primary: Superiority of darolutamide + ADT over placebo + ADT in rPFS Secondary: OS, time to CRPC, time to initiation of subsequent antineoplastic therapy, time to PSA progression, PSA undetectable rates (<0.2 ng/mL), time to pain progression (BPI-SF), and safety	Participants with mHSPC	Darolutamide: 443 Placebo: 223	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg, or placebo Concurrently with ADT	Module 5.3.5.1, Report B002412

Clinical phase	Bayer study no / Study name (Orion study no)	Countries/regions	Study period	Study design	Primary and secondary objectives	Study population	Treated participants/ Exposed participants	Treatment and dose	Location / Report no
5.3.5 Reports of Efficacy and Safety Studies - 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (nmCRPC)									
Phase 3	17712 ARAMIS (3104007)	Argentina, Australia, Belarus, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Peru, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, UK, US	FPFV 12SEP2014 Primary completion 03SEP2018 Final OS analysis 15NOV2019 LPLV 14JUN2021	Randomized (2:1), double-blind, placebo-controlled	Primary: Superiority of darolutamide + ADT over placebo + ADT in MFS Secondary: Benefit of darolutamide for OS, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, time to first SSE; safety and tolerability	Participants with CRPC who have undetectable metastases by conventional imaging techniques (i.e. CT, MRI, BS)	Double-blind: Darolutamide: 954 Placebo: 554 Unblinding 30OCT2018: All 170 participants on placebo at the time of unblinding crossed over from placebo to open-label darolutamide	Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a daily dose of 1200 mg, or placebo Concurrently with ADT	Primary completion analysis: 5.3.5.1, Report PH-39723 Final OS analysis: 5.3.5.1, Report PH-41302 Final: Module 5.3.5.1, Report PH-42041
5.3.5 Reports of Efficacy and Safety Studies - 5.3.5.2 Study Reports of Uncontrolled Clinical Studies									
Phase 2	18035 ARADES-EXT (3104002)	Czech Republic, Estonia, Finland, France, UK, US	FPFV 30JUN2011 LPLV 21OCT2015	Extension study for Study 17829	Primary: Long-term safety and tolerability Secondary: Antitumor activity	Participants with mCRPC	76 participants from Study 17829 continued to extension from Phase 1: 19 from Phase 2: 57	Same dose as given in Week 12 of Study 17829. One dose escalation at time of disease progression was allowed.	5.3.5.2, Report R-11102

Clinical phase	Bayer study no / Study name (Orion study no)	Countries/regions	Study period	Study design	Primary and secondary objectives	Study population	Treated participants/ Exposed participants	Treatment and dose	Location / Report no
5.3.5 Reports of Efficacy and Safety Studies - 5.3.5.4 Other Study Reports and Related Information									
Phase 3B	20321	As of 30JAN2024: Argentina, Australia, Austria, Belarus, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russia, Serbia, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, UK, and US	FPFV 20OCT2020 Ongoing	Open-label, single arm, roll-over study	Primary: Continuation of treatment and safety Secondary: Documentation of tolerability	Participants previously enrolled and on darolutamide treatment in any Bayer-sponsored feeder study	As of 30JAN2024: 676 total: 409 from ARAMIS, 266 from ARASENS, and 1 from ARAFOR 286 ongoing with treatment	Darolutamide at the dose and schedule specified in the feeder study protocol Any other medication as specified in the feeder study protocol used in combination with darolutamide	No study report available

2.3.2. Pharmacokinetics

No new pharmacokinetics studies have been submitted in support of this application.

2.3.3. Pharmacodynamics

No new pharmacodynamics studies have been submitted in support of this application.

2.3.4. Discussion and conclusion on clinical pharmacology

No new clinical pharmacology data are available for this application.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The selected dosing regimen is **600 mg (2 tablets of 300 mg) BID** with food, equal to a total **daily dose of 1200 mg**.
This darolutamide dosing regimen is currently approved for the treatment of patients with nmCRPC and in combination with docetaxel in patients with mHSPC with the same recommended dose. Patients receiving darolutamide should also receive an LHRH agonist or antagonist (GnRH analog) concurrently or should have had an orchiectomy.

2.4.2. Main study

Study ARANOTE

Study ARANOTE is a randomized, double-blind, placebo-controlled phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC).

Methods

Study design:

Approximately 665 participants, who met the eligibility criteria, including confirmation of metastatic disease by BICR, were planned to be randomized in a 2:1 ratio to receive 1 of the following study drugs:

- Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg
- Placebo darolutamide matched tablets in appearance, twice daily with food

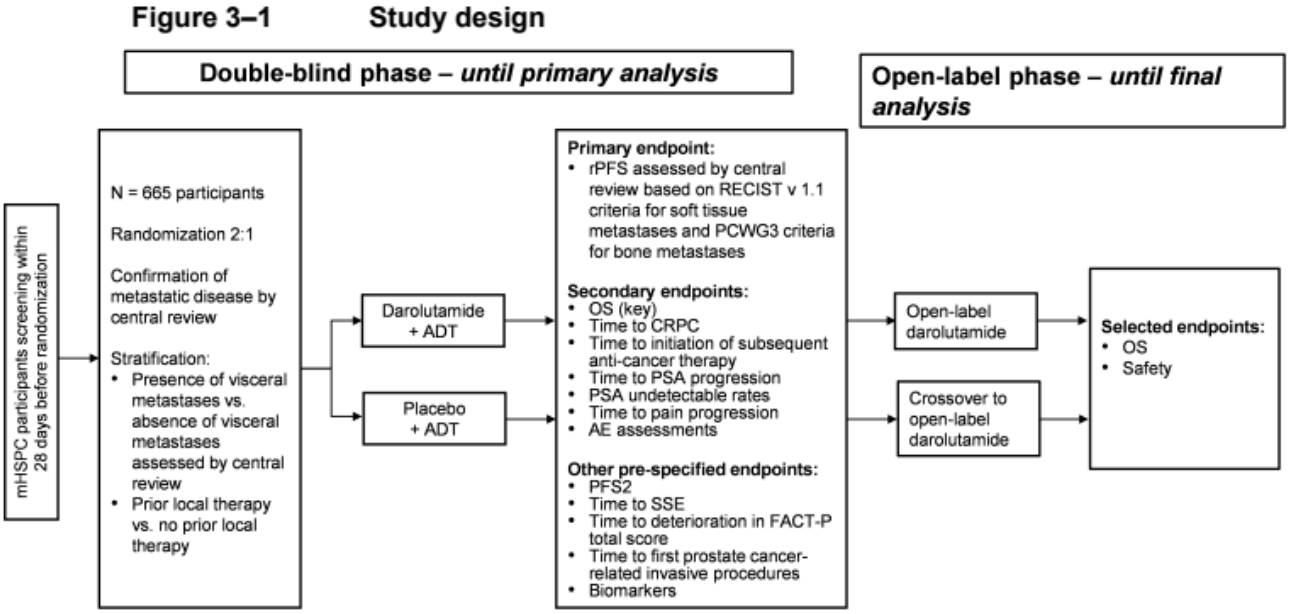
Participants were stratified at randomization as follows:

- Presence of visceral metastases vs. absence of visceral metastases assessed by blinded independent central review (BICR)
- Prior use of local therapy vs. no prior local therapy

All participants were required to receive ADT of the investigator's choice (LHRH agonist/antagonists or orchiectomy) as background therapy, started no earlier than 12 weeks before randomization, on a continuous basis. For participants receiving LHRH agonists, treatment in combination with a first-generation antiandrogen for at least 14 days prior to randomization was recommended. The first-generation antiandrogen was discontinued before study drug start.

An independent DMC monitored the unblinded safety data on a regular basis throughout the double-blind period.

Figure 1 Study design



ADT=Androgen deprivation therapy; AE=Adverse event; CRPC=Castration-resistant prostate cancer; FACT-P=Functional Assessment of Cancer Therapy-Prostate; mHSPC=Metastatic hormone-sensitive prostate cancer; OS=Overall survival; PCWG3=Prostate Cancer Working Group 3; PFS2=Progression-free survival 2; PSA=Prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=Radiological progression-free survival; SSE=Symptomatic skeletal event

Study participants

Table 5 Overview of the Key inclusion criteria

Table 3–1 Overview of key inclusion and exclusion criteria

Key inclusion criteria	
Study population (and protocol definition)	mHSPC; Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by BICR.
Histology/cytology	Histologically or cytologically confirmed adenocarcinoma of the prostate
Sex and age	Males ≥18 years of age
Prior/concomitant therapy	Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first generation antiandrogen, but not earlier than 12 weeks before randomization. For participants receiving LHRH agonists, treatment in combination with a first generation antiandrogen for at least 14 days prior to randomization was recommended. First generation antiandrogen had to be discontinued at least 1 day before study treatment start.
ECOG PS	0, 1, or 2
Organ function	Adequate bone marrow, liver, and renal function
Key exclusion criteria	
Small cell, ductal or neuroendocrine carcinoma of the prostate	• Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate
Brain metastases	• Known brain/leptomeningeal metastases
Excluded prior therapy	• LHRH agonist/antagonists started >12 weeks before randomization except neoadjuvant and/or adjuvant therapy for a duration ≤24 months and completed ≥12 months prior to randomization • Second-generation AR inhibitors, such as enzalutamide, darolutamide, apalutamide, or other investigational AR inhibitors • CYP17 enzyme inhibitor, such as abiraterone acetate or oral ketoconazole, as anticancer treatment for prostate cancer • Chemotherapy, including docetaxel or immunotherapy for prostate cancer • Use of systemic corticosteroid with a dose greater than the equivalent of 10 mg of prednisone/day within 28 days prior to randomization • Radiopharmaceuticals • Any other anticancer treatment for prostate cancer, excluding local therapies and ADT • Radiotherapy (EBRT, brachytherapy) within 2 weeks before randomization

Table 3–1 Overview of key inclusion and exclusion criteria

Cardiac history	Any of the following within 6 months before the first drug administration: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure (NYHA Class III or IV)
Other medical history	Prior malignancy within 5 years before randomization
	Active viral hepatitis, HIV infection with detectable viral load, or chronic liver disease with a need for treatment
	Uncontrolled hypertension despite medical management
	Gastrointestinal disorder or procedure that significantly interferes with the absorption of the study drug
	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 participant and/or his compliance with study procedures, or may interfere with the participant's participation in the study or evaluation of the study results

ADT=Androgen deprivation therapy; AR=Androgen receptor; BICR=Blinded independent central review; CT=Computed tomography; CYP17=Cytochrome P17; EBRT= External beam radiation therapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HIV=Human immunodeficiency virus; LHRH=Luteinizing hormone-releasing hormone; mHSPC=Metastatic hormone-sensitive prostate cancer; MRI=Magnetic resonance imaging; NYHA=New York Heart Association

Patients with a medical history of seizure were allowed to enter the study, and 1 patient (0.2%) was enrolled in the darolutamide arm.

Treatments

The test product was darolutamide (BAY 1841788), administered 600 mg (2 tablets of 300 mg) BID with food, equal to a total daily dose of 1200 mg.

Placebo matching darolutamide was administered according to the same protocol as darolutamide.

Table 6 Study drug administration

Table 3–4 Study drugs administered

Study Drug Name	**Darolutamide**	**Placebo**
Type	Drug	Drug
Dose Formulation	Film-coated tablet	Film-coated tablet
Unit Dose Strength	300 mg/tablet	Not applicable
Dosage Levels	600 mg BID	BID
Route of Administration	Oral	Oral
Use	Active test drug	Inactive comparator
Packaging and Labeling	Study drug was provided in 150 mL HDPE bottles with child resistant closure, each containing 140 tablets. Each bottle was labeled as required per country requirement.	Study drug was provided in 150 mL HDPE bottles with child resistant closure, each containing 140 tablets. Each bottle was labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Darolutamide (International Nonproprietary Name), BAY 1841788	Placebo to darolutamide

BID=twice daily; HDPE=High-density polyethylene

The start of the treatment period was defined by the first administration of study drug. During treatment period, participants were evaluated with regular clinic visits every 12 weeks (±7 days) for efficacy and safety. In the double-blind period, participants received study drug until documented radiological disease progression assessed by central review, unacceptable toxicity or until any other withdrawal criteria is met. An independent Data Monitoring Committee (DMC) monitored the unblinded safety data on a regular basis throughout the double-blind period.

In addition to the study drug, all participants (except for 1 in the darolutamide arm) received concomitant ADT (LHRH agonist/antagonists) on a continuous basis and/or had orchiectomy.

For participants receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 14 days prior to randomization is recommended. First generation anti–androgen was discontinued one day before study treatment start.

Objectives

Outcomes/endpoints

Table 7 Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS in participants with mHSPC	• rPFS assessed by central review based on RECIST v. 1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases
Secondary	
• To evaluate efficacy of darolutamide in addition to ADT compared to placebo plus ADT by improving OS, time to CRPC, time to initiation of subsequent anticancer therapy, time to PSA progression, and undetectable PSA rates	• OS – key secondary endpoint • Time to CRPC • Time to initiation of subsequent anticancer therapy • Time to PSA progression • PSA undetectable rates (<0.2 ng/mL)
• To estimate the participant's quality of life benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving (delaying) symptomatic time to pain progression	• Time to pain progression (BPI-SF)
• To assess the safety of darolutamide in addition to ADT compared to placebo plus ADT in participants with mHSPC	• AE assessments using NCI-CTCAE (v. 5.0)
Other prespecified	
• To further evaluate efficacy of darolutamide in addition to ADT compared to placebo plus ADT by progression-free survival 2 as assessed by the investigator (PFS2)	• PFS2
• To estimate the participant's quality of life[a] benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving time to first SSE	• Time to SSE
• To investigate tumor[b] and circulating biomarkers with the aim of elucidating the molecular profile of the participants potentially related to response to darolutamide[c]	• Alterations of markers related to prostate cancer and AR inhibition such as AR alterations, alternative AR splice variants (e.g. AR V7), PTEN loss[c]
• To assess changes in tumor molecular status in circulating tumor DNA obtained before, during treatment and after progression on darolutamide, with the aim of elucidating the molecular profile, modifiers of response and acquired resistance to darolutamide[c]	
• To further investigate the study drug and similar drugs (e.g. mode-of-action-related effects, safety) and to further investigate pathomechanisms	• Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)[b,c]

Objectives	Endpoints
deemed relevant to cancer and associated health problems[b,c]	
• To estimate the participant's quality of life benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving (delaying) time to deterioration in FACT-P total score	• Time to deterioration in FACT-P total score
• To estimate the benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving time to first prostate cancer-related invasive procedures	• Time to first prostate cancer-related invasive procedure

ADT=Androgen deprivation therapy; AE=Adverse event; AR=Androgen receptor; BPI-SF=Brief Pain Inventory – Short Form; CRPC=Castration-resistant prostate cancer; FACT-P=Functional Assessment of Cancer Therapy-Prostate; mHSPC=Metastatic hormone-sensitive prostate cancer; NCI-CTCAE (v. 5.0)=National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0); OS=Overall survival; PCWG3=Prostate Cancer Working Group 3; PFS2=Progression-free survival 2; PSA=Prostate-specific antigen; PTEN=Phosphatase and tensin homolog; RECIST v. 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; rPFS=Radiological progression-free survival; SAP=Statistical Analysis Plan; SSE=Symptomatic skeletal event

a: Not a patient reported outcome.

b: Not applicable for China.

c: The results from the exploratory biomarker analyses will be reported in a separate biomarker report, as per the SAP

Estimands

Table 8 Estimands

Estimands:

	Primary estimand	Secondary estimands
Scientific question of interest	What is the treatment effect based on rPFS for darolutamide in addition to ADT vs. placebo plus ADT in participants with mHSPC, regardless of study treatment discontinuation?	What is the treatment effect based on OS for darolutamide in addition to ADT vs. placebo plus ADT in participants with mHSPC, regardless of study treatment discontinuation or start of subsequent anticancer therapy?
Treatment	Darolutamide (BAY 1841788) 600 mg BID vs. placebo matching darolutamide	Darolutamide (BAY 1841788) 600 mg BID vs. placebo matching darolutamide
Population	Randomized participants as defined by the protocol inclusion/exclusion criteria	Randomized participants as defined by the protocol inclusion/exclusion criteria
Variable	rPFS assessed by central review based on RECIST v. 1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases	OS is defined as the time from the date of randomization to the date of death from any cause
Intercurrent events (strategy)	Early discontinuation of study treatment (treatment policy strategy) Start of subsequent anticancer therapy (hypothetical strategy)	Early discontinuation of study treatment (treatment policy strategy) Start of subsequent anticancer therapy (treatment policy strategy)
Population-level summary	rPFS analyzed with a log-rank test and Cox regression proportional hazard model, stratified by the same factors as used for randomization	OS analyzed with a log-rank test and Cox regression proportional hazard model, stratified by the same factors as used for randomization.

ADT=Androgen deprivation therapy; BID=Twice daily; mHSPC=Metastatic hormone-sensitive prostate cancer; OS=Overall survival; PCWG3=Prostate Cencer Working Group 3; RECIST v. 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; rPFS=Radiological progression-free survival

Sample size

Statistical Hypotheses:
The null hypothesis that there is no difference in rPFS between treatment arms, which is equivalent to a hazard ratio (HR) of 1, was tested against the alternative hypothesis that the HR of darolutamide over placebo is below 1.

Sample Size Determination:
Assuming a one-sided alpha of 0.025 for rPFS, a power of 90%, and a randomization ratio of 2:1 between the experimental and control arms, 214 events were required to detect a 60% increase in median time of rPFS (HR 0.625).
Assuming an exponential distribution of rPFS events and a control arm median time of 20 months, the active arm median would be approximately 32 months, which is a 60% increase in median time.
The expected study duration was approximately 36 months, assuming approximately 665 participants were randomized at a rate of 45 participants per month, an enrolment ramp-up time of 6 months, approximately 18 months until randomization was completed, a dropout rate of 33% for rPFS follow-up, exponentially distributed event times, and 20-month median time of rPFS for the control group.
Assuming a 25% screening failure rate, approximately 886 screened participants would lead to 665 randomized participants.

Randomisation

ARANOTE is a randomized, double-blind, placebo-controlled Phase 3 study to determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving radiological progression-free survival (rPFS) in participants with mHSPC.

After an up to 28-day screening period, participants who satisfied all eligibility criteria were randomized in a 2:1 ratio to receive one of the following study drugs:
• Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg
• Placebo darolutamide matched tablets in appearance, twice daily with food.

Participants were stratified at randomization as follows:
- visceral metastases and
- prior local therapy at study entry.

Blinding (masking)

Participants were randomized in a 2:1 allocation ratio to receive study drug (darolutamide or matching placebo) in a double–blind fashion such that neither the investigator/study site personnel nor the sponsor, nor the participant would know which study drug was being administered.

Treatment assignments of participants randomized to study drug were done centrally using IWRS. A computer-generated randomization list was generated by the sponsor or delegate for random assignments and provided to the IWRS vendor. The randomization number was assigned to the participant through the IWRS based on information supplied by the investigator at the time of randomization.

Darolutamide and placebo were identical in appearance in order to preserve blinding. To maintain the blind, study drugs were packaged in bottles labelled with a unique kit number. The study kit number was assigned to the participant through the IWRS.

The DMC regularly reviewed safety data and certain efficacy data in an unblinded manner.

Statistical methods

Analysis set

The populations for analyses are defined in Table 9

Table 9 Populations for analyses

Table 3–5 Populations for analyses

Population	Description
Enrolled	All participants who signed the ICF.
FAS	All participants who were randomized were included in the FAS. Participants were grouped according to the treatment they were allocated to receive at randomization, irrespective of the actual treatment received.
SAF	All participants who were randomized and took at least 1 dose of the study drug were included in the SAF. Participants were analyzed according to the study drug they actually received.

FAS=Full analysis set; ICF=Informed consent form; SAF=Safety analysis set

The efficacy analyses were performed in the FAS, including all participants who were randomized. Following the **intent to treat principle**, the participants in this set were grouped according to the planned treatment they were allocated to receive at randomization, irrespective of actual treatment.

The primary endpoint (rPFS) was defined as the time from the date of randomization to the date of disease progression (PD) in malignant soft tissue lesions, PD in malignant bone lesions, or death due to any cause, whichever occurred first. The null hypothesis, stating that there is no difference in rPFS between treatment arms, which is equivalent to a hazard ratio (HR) of 1, was tested against the alternative hypothesis that the HR of darolutamide over placebo is below 1.

Analysis of rPFS:
All randomized participants (FAS) were included in the primary analysis of rPFS. The analysis will be performed when approximately 214 events of rPFS are observed. The primary analysis will be a stratified log–rank test with the same stratification factors as used for randomization (from by central review IWRS). The HR (darolutamide group/placebo) for rPFS and its 95% confidence interval will be calculated using the Cox model, stratified by the same factors as stated above. Kaplan–Meier (KM) estimates for rPFS will be presented for each treatment group. The KM estimates at time points such as 3 months, 6 months, etc., together with corresponding 95% confidence intervals (CIs) and the differences of these estimates between the darolutamide group and the placebo group will be presented. The overall 1–sided type I error rate for the analysis of rPFS is 0.025. No interim analyses of rPFS are planned.

The secondary efficacy endpoints were tested for statistical significance with the hierarchical gatekeeping procedure: OS, time to initiation of subsequent anticancer therapy, time to castration-resistant prostate cancer (CRPC), time to prostate-specific antigen (PSA) progression, PSA undetectable rate, and time to pain progression. The secondary efficacy endpoints were to be tested only if the primary endpoint, rPFS, was statistically significant at a one-sided alpha level of 0.025.

The key secondary endpoint (OS) was defined as the time from the date of randomization to the date of death from any cause. A positive trend in favour of darolutamide was observed with respect to the key secondary endpoint, OS. Since OS was not statistically significant at the prespecified alpha significance level of 0.0185 (one-sided) based on 163 OS events observed, the other secondary endpoints were not formally tested for statistical significance according to the hierarchical gatekeeping procedure.

The frequency of adverse events (AEs) were assessed in terms of their seriousness, intensity (severity per the National Cancer Institute Common Terminology Criteria for AEs [NCI-CTCAE], v. 5.0), and their relationship to the study drugs.

Analysis of secondary endpoints:
The secondary efficacy endpoints were analyzed in the FAS population at the time of primary analysis unless otherwise specified in SAP. Time–to–event endpoints was analyzed using same method as the primary efficacy variable. The stratified log–rank test with randomization stratification factors was used to compare treatment effect. Hazard ratio and 95% CI were provided using the Cox model stratified by the same factors as stated above. Detailed analysis methods and the plan for type 1 error control for secondary endpoints were specified in SAP. Only overall survival were tested at the final analysis time point, when the open-label phase ended. Therefore, during the open-label period, data collection would continue with recording of survival status.

Hierarchical testing scheme of the secondary variables

The secondary efficacy endpoints were tested for statistical significance using a hierarchical gatekeeping procedure in the following order: OS (key secondary endpoint), time to initiation of subsequent anticancer therapy, time to CRPC, time to PSA progression, PSA undetectable rates, and time to pain progression.
The secondary endpoints were tested only if the primary endpoint, rPFS, was statistically significant at a one-sided alpha level of 0.025.

Changes in planned analyses prior to unblinding or database lock

Changes from the statistical analyses planned in the protocol to the final SAP are described in Table 10. No changes were made to the analyses specified in the final SAP (v. 2.0).

Table 10 Changes to protocol-planned analyses

SAP Section Number[a]	Description of Change	Brief Rationale
4.3.6	Used an increase of 2 or more points in the WPS score from nadir for the definition of pain progression.	Change from baseline to nadir in the definition of pain progression was based on FDA feedback on the ARASENS study.
	Added initiation of short- or long-acting opioid use for malignant disease for ≥7 consecutive days to the definition of pain progression.	Based on FDA feedback to include opioid use for malignant disease for ≥7 consecutive days during treatment in the definition of time to pain progression.
	Used WPS ≥5 in the definition of pain progression.	Change of WPS ≥5: based on FDA feedback on ARASENS study, and a publication (Atkinson et al. 2010).

FDA=Food and Drug Administration; SAP=Statistical analysis plan; WPS=Worst pain subscale
a: Changes from the statistical analyses planned in the protocol to the SAP v. 2.0

Subgroup Analyses of efficacy endpoints

Subgroup analyses were conducted for the primary efficacy endpoint rPFS and secondary efficacy endpoint OS based on the FAS population, non-stratified Cox regression model and non-stratified log-rank test were used. Descriptive statistics and HR estimates with 95% CI were provided at least for the subgroups listed below, provided there were a sufficient number of events in total within the subgroup across the treatment arms. Forest plots of the HRs were generated.

- Presence of visceral metastases assessed by central review (Yes vs. No) (from IWRS)
- Received prior local therapy (Yes vs. No) (from IWRS)
- Prior local radiotherapy and/or prostatectomy (Yes, No) (selection provided in Appendix 8.10)

• Age group (<65, 65 – 74, 75 – 84 and ⩾85 years)
• Race (White, Asian, Black or African American, Other)
• Geographical region
o Asia (China, India, Taiwan)
o Latin America (Brazil, Chile, Peru)
o Europe and Rest of the world (Australia, Canada, Spain, Lithuania, Latvia, New Zealand, Russia, Ukraine, and South Africa)
• Baseline PSA values by median (< median of overall population, ⩾ median of overall population)
• ECOG PS at baseline (=0, ⩾1)
• Gleason score at initial diagnosis (Gleason <8, Gleason ⩾8)
• Disease volume at baseline (high and low)

Results

Disposition and treatment duration:
Of the 889 enrolled participants, 202 participants (22.7%) were screen failures. A total of 669 participants were randomized in a 2:1 ratio to the darolutamide arm (N=446) and placebo arm (N=223) and were included in the FAS. Participants were analyzed for efficacy according to the treatment they were allocated to receive at randomization, irrespective of actual treatment received.

With the exception of 3 participants in the darolutamide arm, all randomized participants received at least 1 dose of the study drug.

The study drug was administered according to the randomized treatment assignment, except for 2 participants randomized to the placebo arm who received at least 1 dose of darolutamide through wrong kit assignment. These 2 participants were included in the darolutamide arm in the analysis of all safety variables.

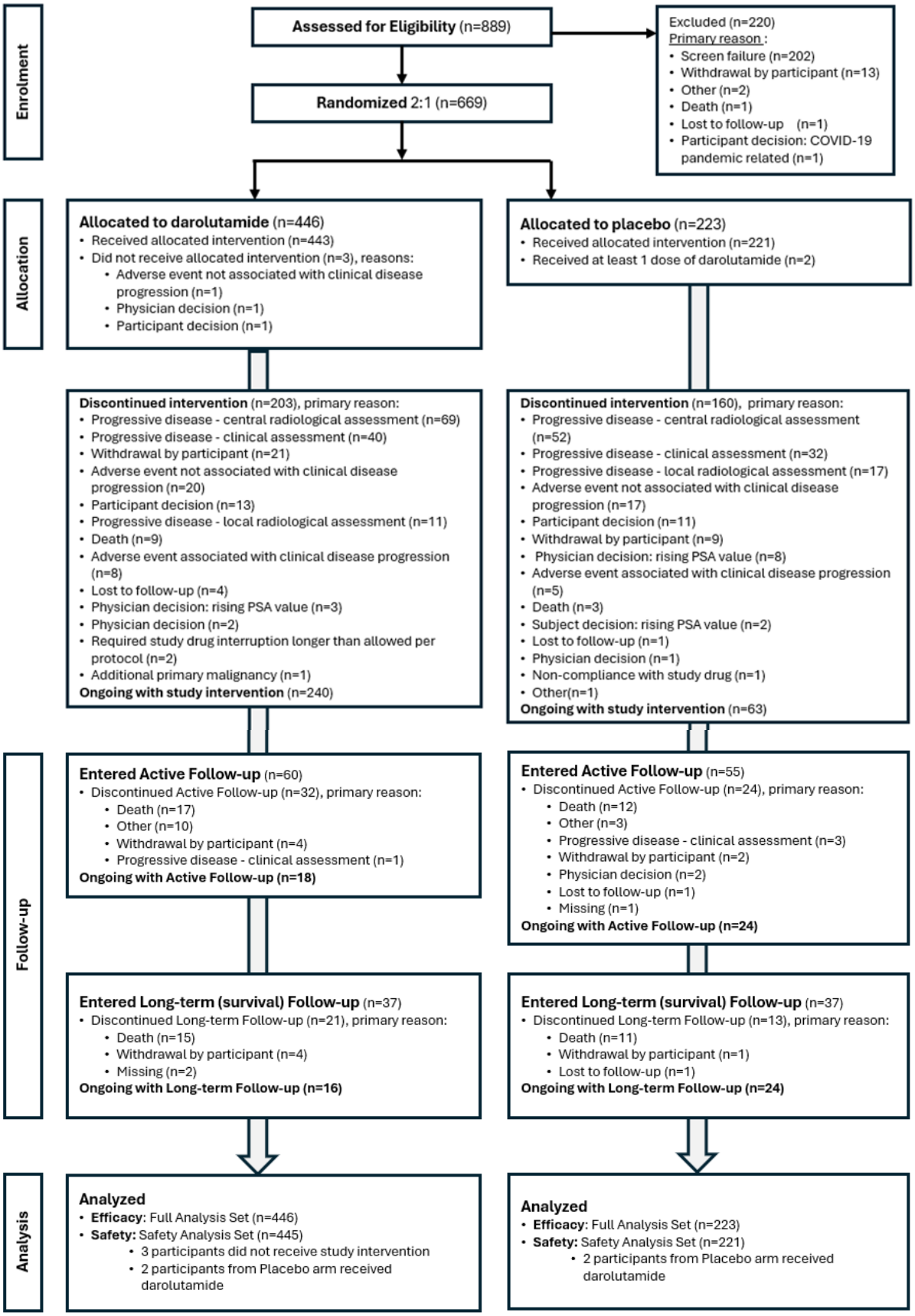
Thus, the SAF includes 445 participants in the darolutamide arm and 221 participants in the placebo arm. As of the database cut-off date for the primary completion analysis (07 JUN 2024), 53.8% of the randomized participants in the darolutamide arm and 28.3% in the placebo arm remained on study treatment in the FAS.

The study drug was permanently discontinued in a lower percentage of participants in the darolutamide arm than in the placebo arm (45.5% vs. 71.7% in the FAS, respectively). The most common reason for treatment discontinuation in both treatment arms was progressive disease - central radiological assessment (15.5% and 23.3% of participants in the darolutamide and placebo arms, respectively).

The overall median time under study treatment was longer in the darolutamide arm than in the placebo arm (24.2 vs. 17.3 months, respectively). Overall, a higher percentage of participants had ≥24 months study drug exposure in the darolutamide arm than in the placebo arm (50.3% vs. 34.4%, respectively).

Participant flow

Figure 2 Participant disposition at the time of the database cut-off date (07 June 2024)



As of the database cut-off date, 4.0% of the participants in the darolutamide arm and 10.8% in the placebo arm were ongoing in the active follow-up period and 3.6% vs. 10.8% of the participants, respectively, were ongoing in survival follow-up.

Recruitment

The study started enrolling participants on 23 FEB 2021 and is being conducted in 15 countries/regions, divided into 3 regional subgroups:

• Europe/ROW: Australia, Canada, Latvia, Lithuania, New Zealand, Russia, South Africa, Spain, and Ukraine

• Asia: mainland China, India, and Taiwan

• Latin America: Brazil, Chile, and Peru.

Enrolment was completed on 09 AUG 2022. (Study completion date: 2025-09-26)

Conduct of the study

Protocol deviations

Overall, important protocol deviations occurred with similar frequency between the treatment arms (Table 12).

Table 11 Number of participants with important protocol deviation (FAS)

Protocol Deviation Category Subcategory	Darolutamide N=446 n (%)	Placebo N=223 n (%)
Participants with any important deviation[a]	299 (67.0)	163 (73.1)
Study conduct / procedures	256 (57.4)	137 (61.4)
Screening	153 (34.3)	85 (38.1)
Study assessment	119 (26.7)	81 (36.3)
Study restrictions/withdrawal criteria	34 (7.6)	19 (8.5)
Inclusion/exclusion criteria	11 (2.5)	5 (2.2)
Dose formulation/dose administration	7 (1.6)	5 (2.2)
Informed consent	46 (10.3)	20 (9.0)
Presence/absence	38 (8.5)	16 (7.2)
Signature/date	8 (1.8)	4 (1.8)
Version	2 (0.4)	2 (0.9)
Safety	37 (8.3)	17 (7.6)
Reporting/follow-up	24 (5.4)	11 (4.9)
Recording	14 (3.1)	7 (3.1)
Investigational product	26 (5.8)	13 (5.8)
Handling/storage/retention	11 (2.5)	9 (4.0)
Dispensing/accountability	15 (3.4)	4 (1.8)
Supply	0	1 (0.4)
Other	20 (4.5)	16 (7.2)
Other	20 (4.5)	16 (7.2)

COVID-19=Coronavirus disease 2019; FAS=Full analysis set; N=Total number of participants (100%); n=Number of participants with event

a: Participants may have had >1 protocol deviation but were only counted once within each deviation category. Important protocol deviations associated with the COVID-19 pandemic are included in this table.

Baseline data

Study population:

Table 12 Key demographics and baseline characteristics (FAS)

	Darolutamide N=446	Placebo N=223	Total N=669
Age at screening (years)			
N	446	223	669
Mean (SD)	69.6 (8.8)	69.2 (8.9)	69.5 (8.8)
Median	70.0	70.0	70.0
Min, Max	43, 93	45, 91	43, 93
Age category (years), n (%)			
<65	118 (26.5)	65 (29.1)	183 (27.4)
65–74	193 (43.3)	96 (43.0)	289 (43.2)
75–84	117 (26.2)	52 (23.3)	169 (25.3)
≥85	18 (4.0)	10 (4.5)	28 (4.2)
Geographical region, n (%)			
Europe/ROW	186 (41.7)	88 (39.5)	274 (41.0)
Asia	141 (31.6)	63 (28.3)	204 (30.5)
Latin America	119 (26.7)	72 (32.3)	191 (28.6)
Race, n (%)			
White	251 (56.3)	125 (56.1)	376 (56.2)
Black or African American	41 (9.2)	24 (10.8)	65 (9.7)
Asian	144 (32.3)	65 (29.1)	209 (31.2)
Other[a]	10 (2.2)	9 (4.0)	19 (2.8)
Ethnicity, n (%)			
Hispanic or Latino	104 (23.3)	58 (26.0)	162 (24.2)
Not Hispanic or Latino	334 (74.9)	157 (70.4)	491 (73.4)
Not reported	8 (1.8)	8 (3.6)	16 (2.4)
Body mass index (kg/m^2)			
N	436	221	657
Mean (SD)	25.873 (4.583)	26.191 (4.612)	25.980 (4.592)
Median	25.310	25.800	25.420
Min, Max	15.06, 50.33	14.43, 45.75	14.43, 50.33
Missing	10	2	12

FAS=Full analysis set; Max=Maximum; Min=Minimum; N=Total number of participants (100%); n=Number of participants within category; ROW=Rest of the World; SD=Standard deviation

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

Note: Data collection for race and ethnicity was not allowed in some countries/regions due to local regulations.

Baseline disease characteristics:

Table 13 Key baseline disease characteristics (FAS)

	Darolutamide N=446	Placebo N=223	Total N=669
Extent of metastatic disease at study entry[a], n (%)			
M1a	17 (3.8)	10 (4.5)	27 (4.0)
M1b	344 (77.1)	171 (76.7)	515 (77.0)
M1c	85 (19.1)	42 (18.8)	127 (19.0)
Visceral metastases assessed by BICR (from IWRS), n (%)			
Present	53 (11.9)	27 (12.1)	80 (12.0)
Absent	393 (88.1)	196 (87.9)	589 (88.0)
Prior local therapy (from IWRS), n (%)			
Yes	80 (17.9)	40 (17.9)	120 (17.9)
No	366 (82.1)	183 (82.1)	549 (82.1)
Stage of prostate cancer at initial diagnosis (TNM classification), n (%)			
Stage I	6 (1.3)	6 (2.7)	12 (1.8)
Stage II	26 (5.8)	7 (3.1)	33 (4.9)
Stage III	31 (7.0)	17 (7.6)	48 (7.2)
Stage IV A	37 (8.3)	15 (6.7)	52 (7.8)
Stage IV B	317 (71.1)	168 (75.3)	485 (72.5)
Unknown	29 (6.5)	10 (4.5)	39 (5.8)
Recurrent[b]	100 (22.4)	45 (20.2)	145 (21.7)
De novo[b]	317 (71.1)	168 (75.3)	485 (72.5)
Stage of prostate cancer at study entry (TNM classification), n (%)			
Stage IVB	446 (100.0)	223 (100.0)	669 (100.0)
Gleason score at initial diagnosis of prostate cancer, n (%)			
<8	122 (27.4)	67 (30.0)	189 (28.3)
≥8	311 (69.7)	146 (65.5)	457 (68.3)
Missing/not assessed	13 (2.9)	10 (4.5)	23 (3.4)
ECOG PS, n (%)			
0	235 (52.7)	98 (43.9)	333 (49.8)
1	199 (44.6)	117 (52.5)	316 (47.2)
2	12 (2.7)	8 (3.6)	20 (3.0)
Prior local radiotherapy/prostatectomy[c], n (%)			
Yes	87 (19.5)	50 (22.4)	137 (20.5)
No	359 (80.5)	173 (77.6)	532 (79.5)
PSA at baseline (central laboratory) (µg/L)			
n	436	219	655
Mean (SD)	322.782 (1192.906)	301.324 (951.758)	315.607 (1117.389)
Median	21.395	21.210	21.290
Min, Max	0.02, 15915.00	0.02, 8533.00	0.02, 15915.00
Missing (n)	10	4	14
Testosterone at baseline (central laboratory), n (%)			
<1.73 nmol/L (<0.5 ng/mL)	219 (49.1)	103 (46.2)	322 (48.1)
≥1.73 nmol/L (≥0.5 ng/mL)	213 (47.8)	115 (51.6)	328 (49.0)
Missing	14 (3.1)	5 (2.2)	19 (2.8)
Disease volume at baseline[d], n (%)			
High	315 (70.6)	157 (70.4)	472 (70.6)
Low	131 (29.4)	66 (29.6)	197 (29.4)

BICR=Blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FAS=Full analysis set; IWRS=Interactive web response system; Max=Maximum; Min=Minimum; N=Total number of participants (100%); n=Number of participants within category; PSA=Prostate-specific antigen; SD=Standard deviation; TNM=Tumor, Node, Metastasis

a: TNM classification system categories for the extent of metastatic disease at study entry (M1) were defined as:
M1a=Nonregional lymph nodes metastases only.
M1b=Bone metastases with or without lymph node metastases.
M1c=Visceral metastases with or without lymph node metastases or with or without bone metastases.

b: Recurrent is defined as Stage I to IV A and *de novo* is defined as Stage IV B

c: Based on medical review.

d: High-volume disease at baseline was defined as the presence of visceral metastases or 4 or more bone lesions, with at least 1 metastasis beyond the vertebral column and pelvic bones. If none of these criteria were met, the participant had low disease volume at baseline.

Prior anticancer therapy and procedures:

Table 14 ADT (LHRH agonist/antagonist and/or orchiectomy) within the 12 weeks prior to randomization (FAS)

Category	Darolutamide N=446 n (%)	Placebo N=223 n (%)
Number (%) of participants with at least 1 prior ADT	445 (99.8)	221 (99.1)
LHRH agonist/antagonist only	398 (89.2)	197 (88.3)
Orchiectomy only	47 (10.5)	23 (10.3)
LHRH agonist/antagonist and orchiectomy	0	1 (0.4)

ADT=Androgen deprivation therapy; FAS=Full analysis set; LHRH=Luteinizing hormone releasing hormone; N=Total number of participants (100%); n=Number of participants with event
Note: Medications or procedures taken within the 12 weeks prior to randomization are included in this table.

In addition to the study drug, all participants received concomitant ADT, except for 1 participant. That participant received one dose of ADT prior to the start of study treatment and did not receive any further doses of ADT.

Prior local treatment for prostate cancer

Table 15 Prior local treatment for prostate cancer (FAS)

Number of participants (%)	Darolutamide N=446 n (%)	Placebo N=223 n (%)
Primary tumor unresected at study entry	369 (82.7)	182 (81.6)
Prostatectomy	43 (9.6)	25 (11.2)
TURP	38 (8.5)	15 (6.7)
Radiotherapy	13 (2.9)	14 (6.3)
Urethra stricturoplasty	1 (0.2)	0

eCRF=Electronic case report form; FAS=Full analysis set; N=Total number of participants; n=Number of participants with event; TURP=Transurethral resection of the prostate
a: Based on eCRF data.
Note: Local treatments for prostate cancer received before randomization (regardless of when the treatments ended) are included in this table. Participants may have had multiple local treatments for prostate cancer, so a participant may have been counted in more than one local treatment for prostate cancer.

Prior systemic anticancer medications

Table 16 Number of participants who received at least 1 prior systemic anticancer medication (FAS)

Preferred drug names	Darolutamide N=446 n (%)	Placebo N=223 n (%)
Number (%) of participants with at least one prior systemic anticancer medication	212 (47.5)	98 (43.9)
Bicalutamide	202 (45.3)	92 (41.3)
Flutamide	10 (2.2)	6 (2.7)

FAS=Full analysis set; N=Total number of participants; n=Number of participants with event; WHO-DD=World Health Organization Drug Dictionary
WHO-DD v. MAR 2024

Subsequent systemic anticancer medications:

Table 17 Subsequent life-prolonging systemic anticancer medication for prostate cancer, by regimen and preferred drug name based on WHO-DD drug record numb er (FAS)

	Darolutamide N=446	Placebo N=223
Number of participants with 1 or more regimen, n (%)	**66 (14.8)**	**68 (30.5)**
1 regimen	49/66 (74.2)	58/68 (85.3)
>1 regimen	17/66 (25.8)	10/68 (14.7)
Number of participants by type of life-prolonging systemic anticancer medication by preferred drug name (WHO-DD Version 2024MAR), **n (%)**	**66 (14.8)**	**68 (30.5)**
Docetaxel	46 (10.3)	46 (20.6)
Abiraterone, abiraterone acetate	26 (5.8)	21 (9.4)
Enzalutamide	6 (1.3)	12 (5.4)
Apalutamide	3 (0.7)	0
Cabazitaxel	2 (0.4)	1 (0.4)
Radium ra 223 dichloride	2 (0.4)	0
Olaparib	1 (0.2)	0

FAS=Full analysis set; N=Total number of participants; n=Number of participants with event; WHO-DD=World Health Organization Drug Dictionary

Note: Multiple subsequent anticancer therapies for prostate cancer could be started on the same day by one participant so a participant may be counted in more than one therapy. All subsequent life-prolonging systemic anticancer medications for prostate cancer summarized in this table were administered on or after the date of first study treatment. Life-prolonging subsequent therapies for prostate cancer are defined by: abiraterone, apalutamide, enzalutamide, docetaxel, cabazitaxel, radium 223, sipuleucel-T, PSMA-617-Lu-177, rucaparib, and olaparib.

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

Numbers analysed

The **FAS** included all patients randomized to receive darolutamide + ADT (446 patients) and placebo + ADT (223 patients).

Table 18 Number of enrolled and randomized participants by country

Region Sub-region/ Country	Enrolled	Total randomized (darolutamide/ placebo)	Region Sub-region/ Country	Enrolled	Total randomized (darolutamide/ placebo)
Asia			Europe and the rest of the world		
China	113	90 (65/25)	Australia	41	28 (21/7)
India	112	93 (61/32)	Canada	4	2 (1/1)
Taiwan	29	21 (15/6)	Latvia	71	57 (39/18)
Latin America			Lithuania	40	34 (25/9)
Brazil	213	148 (90/58)	New Zealand	14	12 (10/2)
Chile	43	29 (19/10)	Russian Federation	110	83 (49/34)
Peru	21	14 (10/4)	South Africa	22	12 (10/2)
			Spain	21	14 (9/5)
			Ukraine	35	32 (22/10)

Outcomes and estimation

Primary efficacy endpoint: rPFS

As of the database cut-off date for the primary completion analysis, a total of 222 rPFS events had occurred based on BICR.

The percentage of participants with an rPFS event was lower in the darolutamide arm (28.7%) than in the placebo arm (42.2%) Table 20

Table 19 rPFS (FAS) Data cut-off date 07 JUN 2024

	Darolutamide N= 446	Placebo N= 223
Number (%) of participants with event	128 (28.7)	94 (42.2)
Number (%) of participants censored	318 (71.3)	129 (57.8)
rPFS (months)		
Median [95% CI]	A [A, A]	25.0 [19.0, A]
Range (including censored values)	0.03** - 36.2**	0.03** - 35.1**
Range (without censored values)	1.2 - 30.5	1.1 - 26.0
rPFS rate at		
Month 6 [95% CI]	0.930 [0.905; 0.954]	0.892 [0.850; 0.934]
Month 12 [95% CI]	0.831 [0.795; 0.867]	0.741 [0.680; 0.802]
Month 18 [95% CI]	0.774 [0.733; 0.815]	0.588 [0.517; 0.659]
Month 24 [95% CI]	0.703 [0.657; 0.749]	0.521 [0.447; 0.595]
Month 30 [95% CI]	0.645 [0.587; 0.703]	0.462 [0.380; 0.544]
Hazard ratio: (darolutamide/placebo) [95% CI] [a]	0.541 [0.413, 0.707]	
One-sided p-value from log-rank test	<0.0001	

A=Value cannot be estimated due to censored data; BICR=Blinded independent central review; CI=Confidence interval; FAS=Full analysis set; IWRS=Interactive web response system; N=Total number of participants (100%); rPFS=Radiological progression-free survival

** Censored observation.

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

a: Hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and 95% CI were based on Cox Regression Model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).

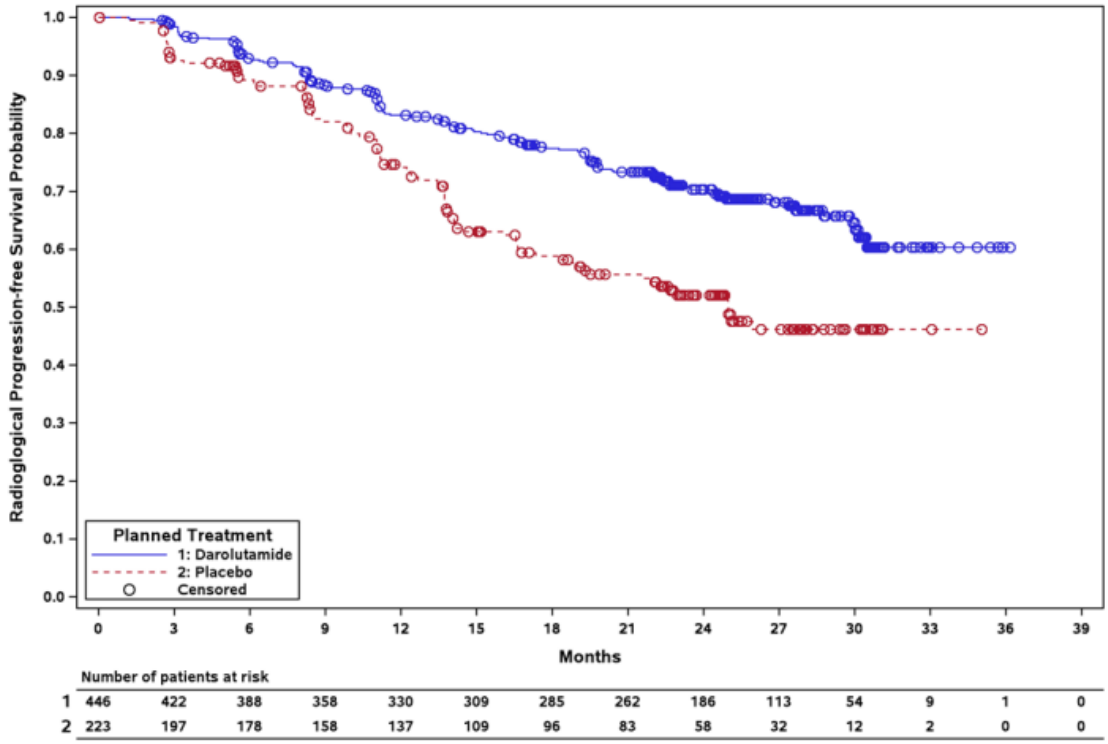
Note: Median, percentile and other 95% CIs were computed using Kaplan-Meier estimates.

Progression of disease was based on data from BICR.

The most commonly observed rPFS event was radiological progression in soft tissue (14.8% in the darolutamide arm vs. 19.3%, in the placebo arm) followed by radiological progression in bone (7.4% vs. 16.6%), and death (6.5% vs. 6.3%) (data not shown)

Table 20 Kaplan-Meier curves of rPFS (FAS) (DCOD)07 JUN 2024

Figure 3–1 Kaplan-Meier curves of rPFS (FAS)



FAS=Full analysis set; rPFS=Radiological progression-free survival
Note: At risk patient counts were calculated as the start of the timepoint.

Secondary efficacy endpoints:

Table 21 Results of secondary efficacy endpoints (FAS) Data cut-off date 07 JUN 2024

Table 3–7 Results of secondary efficacy endpoints (FAS)

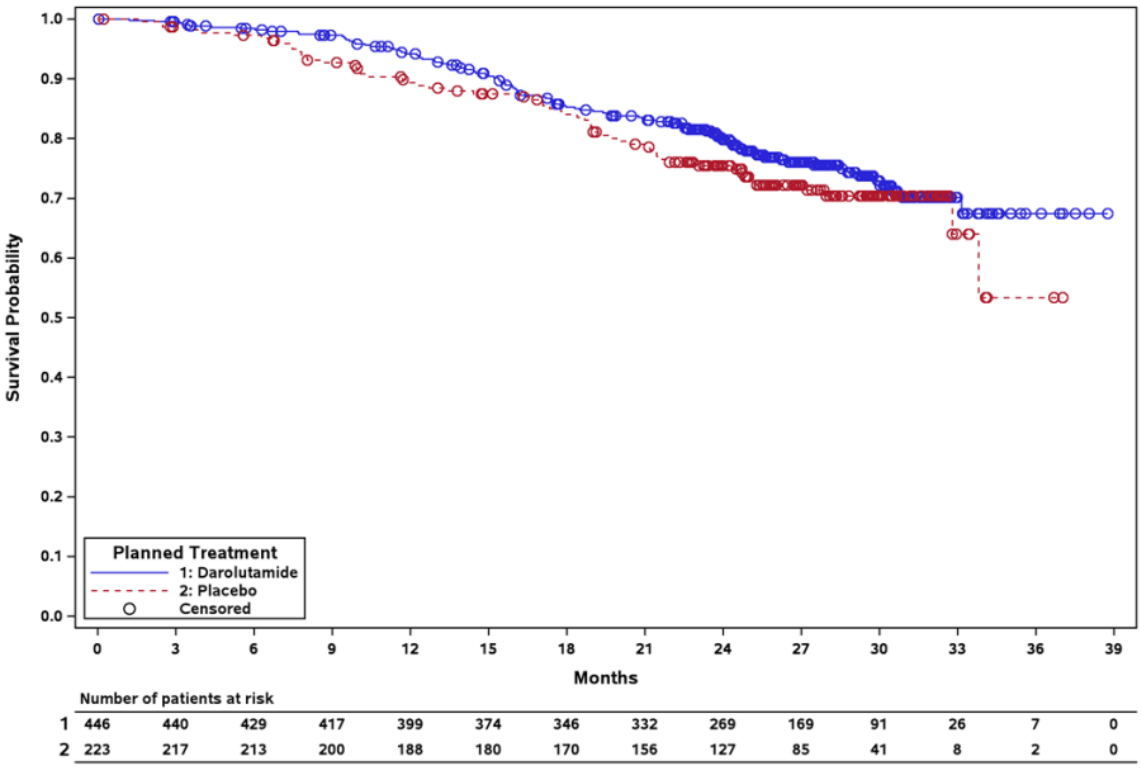
	OS (key efficacy endpoint)		Time to initiation of subsequent anticancer therapy [a]		Time to CRPC		Time to PSA progression		PSA undetectable rates		Time to pain progression	
	Daro N=446	Placebo N=223	Daro N=446	Placebo N=223	Daro N=446	Placebo N=223	Daro N=446	Placebo N=223	Daro N= 425 [e]	Placebo N=211 [e]	Daro N=446	Placebo N=223
Number (%) of participants with event	103 (23.1)	60 (26.9)	68 (15.2)	74 (33.2)	154 (34.5)	143 (64.1)	93 (20.9)	108 (48.4)	266 (62.6)[e] [57.8% - 67.2%]	39 (18.5)[e] [13.5% - 24.4%]	124 (27.8)	79 (35.4)
Number (%) of participants censored	343 (76.9)	163 (73.1)	378 (84.8)	149 (66.8)	292 (65.5)	80 (35.9)	353 (79.1)	115 (51.6)	NA	NA	322 (72.2)	144 (64.6)
Median (months) [95% CI] [b]	A [A, A]	A [33.8, A]	A [A, A]	A [27.7, A]	A [A, A]	13.8 [12.0, 16.8]	A [A, A]	16.8 [13.9; 20.1]	NA	NA	A [A, A]	29.9 [29.7, A]
Range (months) including censored values	0.03** - 38.8**	0.2** - 37.0**	0.03 - 38.6**	0.03** - 35.1**	0.03** - 36.2**	0.03** - 35.2**	0.03** - 38.6**	0.03** - 35.1**	NA	NA	0.03 - 38.4**	0.03 - 34.9**
Range (months) without censored values	1.2 - 33.1	1.6 - 33.8	0.03 - 25.9	1.1 - 29.8	0.2 - 28.6	1.1 - 30.4	2.8 - 28.6	2.8 - 28.3	NA	NA	0.03 - 27.6	0.03 - 29.9
HR (Daro vs. Pla) [95% CI] [c]	0.813 [0.591, 1.118]		0.401 [0.288, 0.558]		0.404 [0.321, 0.508]		0.306 [0.231; 0.405]		Rate difference[f] 44.3% [37.4% - 51.2%]		0.721 [0.544; 0.957]	
One-sided p-value [d]	*0.1007*		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*0.0115*	

A=Value cannot be estimated due to censored data; CI=Confidence interval; CRPC=Castration-resistant prostate cancer; Daro=Darolutamide; FAS=Full analysis set; HR=Hazard ratio; IWRS=Interactive web response system; N=Total number of participants (100%); NA=Not applicable; OS=Overall survival; Pla=Placebo; PSA=Prostate-specific antigen; SAP=Statistical analysis plan
** Censored observation
a: Subsequent anticancer therapy was selected as described in the SAP (v. 2.0) (Module 5.3.5.1, Report B002412, Section 8.3 of Section 10.1.9). First subsequent anticancer therapies are summarized in Section 3.1.6.
b: Median and 95% CI were computed using Kaplan-Meier estimates.
c: A hazard ratio <1 indicates superiority of darolutamide over placebo. The HR and 95% CI were based on a Cox regression model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
d: One-sided p-value from stratified log-rank test (IWRS) – Note: Nominal p-values (in italics) are provided for descriptive purposes only.
e: Percentages are based on participants who had a detectable PSA value at baseline: Daro: N=425 (100%); Placebo: N=211 (100%).
f: The rate difference is based on a Cochran-Mantel-Haenszel test comparing between treatment arm, stratified by IWRS stratification factors: by visceral metastases (present vs. absent) and prior local therapy (yes vs. no)

Key secondary efficacy endpoint: OS

At the time of the database cut-off (IA data cut-off date 07 JUN 2024) **163 OS** events had occurred, with a median follow-up time of 25.3 months in the darolutamide arm and 25.0 months in the placebo arm

Figure 3 Kaplan-Meier curves of OS (FAS)



CI=Confidence interval; FAS=Full analysis set; OS=Overall survival
Note:
At risk patient counts were calculated as the start of the timepoint.
OS rates at 12 months and 24 months were 0.942 (95% CI: [0.920; 0.964]) and 0.798 (95% CI: [0.759; 0.837]), respectively, in the darolutamide arm vs. 0.894 (95% CI: [0.853; 0.935]) and 0.755 (95% CI: [0.696; 0.813]), respectively in the placebo arm.

OS update analyses

A final analysis of OS according to the SAP was performed when approximately 180 deaths have been provided with a data cut-off date of 10 Jan 2025.

Table 22 Study 21140 (ARANOTE) Final Overall Survival Results Summary (DCOD 10 JAN 2025)

	OS (key efficacy endpoint)	
	Darolutamide N=446	Placebo N=223
Number (%) of participants with event	115 (25.8%)	70 (31.4%)
Number (%) of participants censored	331 (74.2%)	153 (68.6%)
Median (days) [95% CI] [a]	A [A; A]	A [A; A]
Range (days) (including censored values)	(1** - 1397**)	(7** - 1334**)
Range (days) (without censored values)	(37 - 1181)	(48 - 1171)
OS Rate		
Month 6 [95% CI]	0.984 [0.972; 0.996]	0.973 [0.951; 0.994]
Month 12 [95% CI]	0.942 [0.920; 0.964]	0.894 [0.853; 0.935]
Month 18 [95% CI]	0.853 [0.819; 0.887]	0.841 [0.791; 0.890]
Month 24 [95% CI]	0.798 [0.759; 0.836]	0.756 [0.698; 0.814]
Month 30 [95% CI]	0.736 [0.693; 0.780]	0.694 [0.630; 0.757]
Month 36 [95% CI]	0.714 [0.668; 0.760]	0.644 [0.573; 0.714]
Month 42 [95% CI]	0.687 [0.629; 0.745]	0.610 [0.517; 0.703]
Month 48 [95% CI]	A [A; A]	A [A; A]
HR (Daro vs. Pla) [95% CI] [b]	0.776 [0.577; 1.045]	
One-sided p-value [c]	0.0473	

A=Value cannot be estimated due to censored data; CI=confidence interval; CRPC=castration-resistant prostate cancer; Daro=Darolutamide; FAS=Full analysis set; HR=Hazard ratio; IWRS=interactive web response system; N=Total number of participants (100%); NA=Not applicable; OS=Overall survival; Pla=Placebo; PSA= Prostate-specific antigen

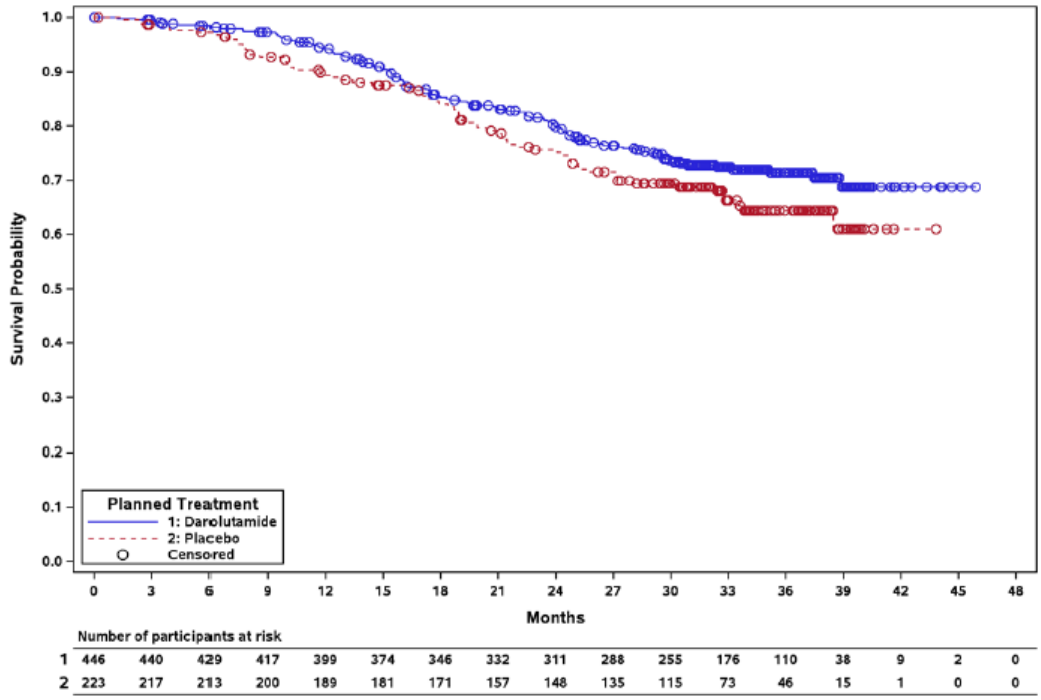
** Censored observation

a: Median and 95% CI were computed using Kaplan-Meier estimates.

b: A hazard ratio <1 indicates superiority of darolutamide over placebo. The HR and 95% CI were based on a Cox regression model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).

c: One-sided p-value from stratified log-rank test.

Figure 4 Kaplan-Meier curves of OS (FAS)



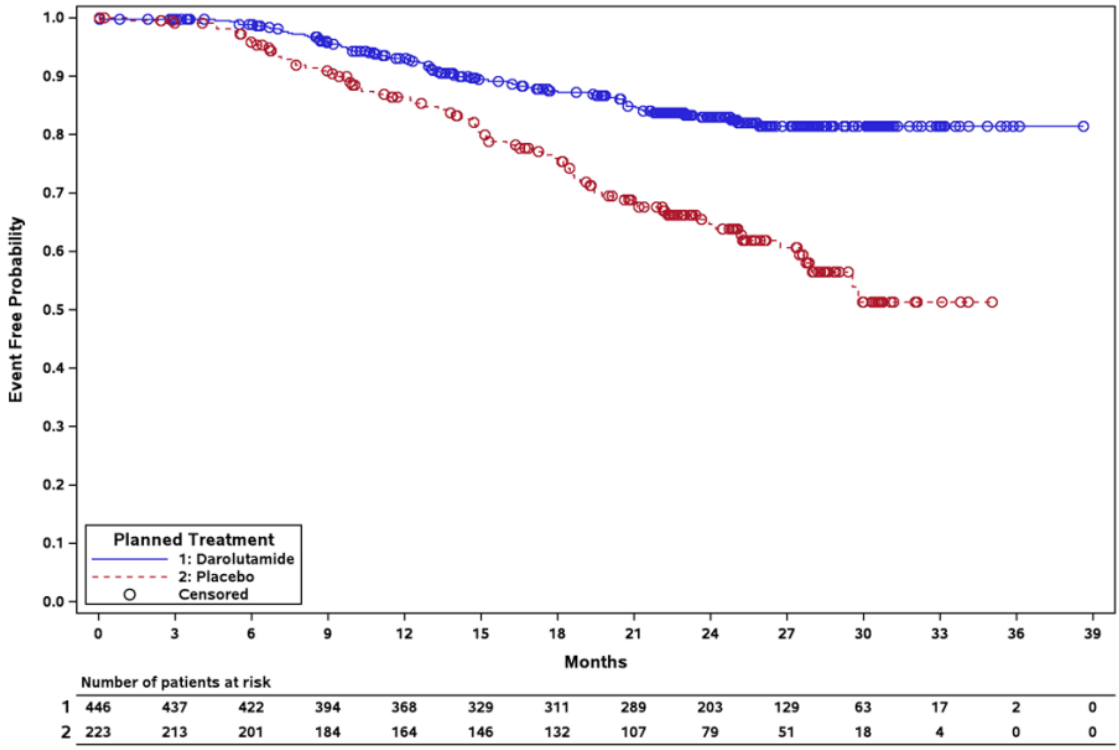
FAS=Full analysis set

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

Time to initiation of subsequent anticancer therapy

There were 15.2% of participants in the darolutamide arm and 33.2% in the placebo arm who started subsequent systemic anticancer therapy for prostate cancer. The Kaplan-Meier curves are presented in Figure 4.

Figure 5 ***Kaplan-Meier curves of*** **Time to initiation of subsequent systemic anticancer therapy For prostate cancer (FAS)**

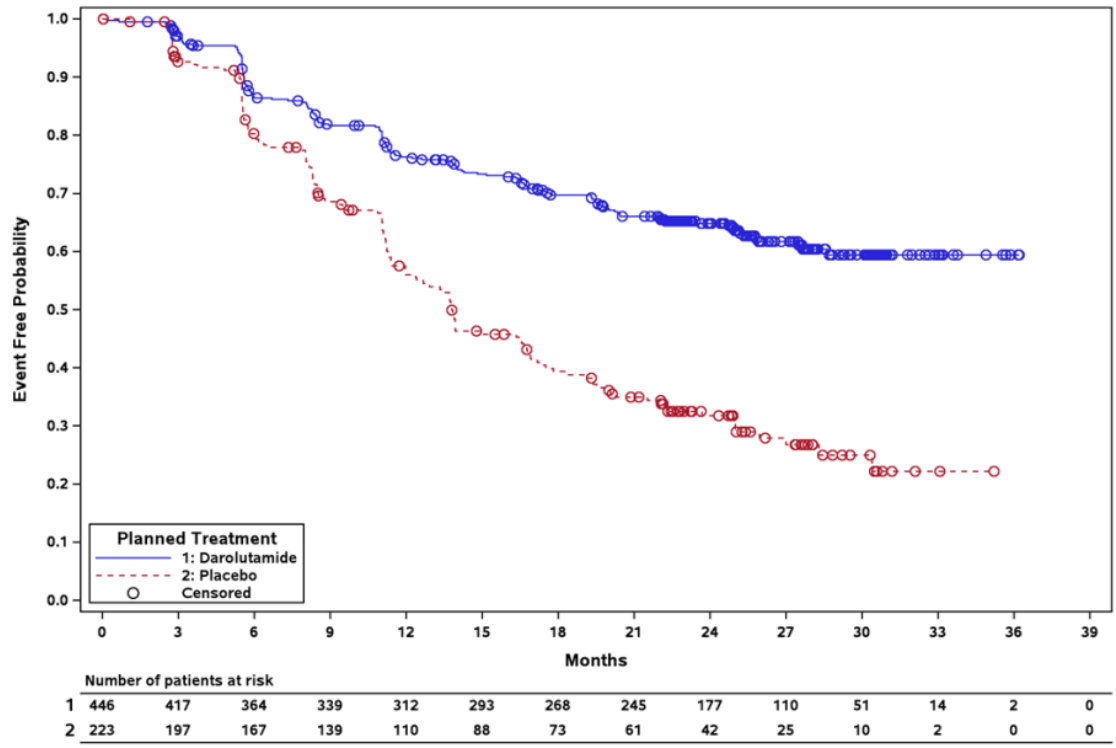


FAS=Full analysis set
Note: At risk patient counts were calculated as the start of the timepoint.

Time to CRPC

Overall, a smaller percentage of participants in the darolutamide arm (34.5%) had progressed to CRPC than in the placebo arm (64.1%) during the study (Table 3–7). Progression to CRPC included PSA progression, radiological progression by bone lesions, radiological progression by soft tissue and visceral lesions, and SSE. In both treatment arms, among the participants progressed to CRPC, the first progression event observed was most commonly PSA progression (55.2% vs. 63.6%, respectively).
The Kaplan-Meier curves are presented in Figure 3–5.

Figure 6 Kaplan-Meier curves of time to CRPC (FAS)



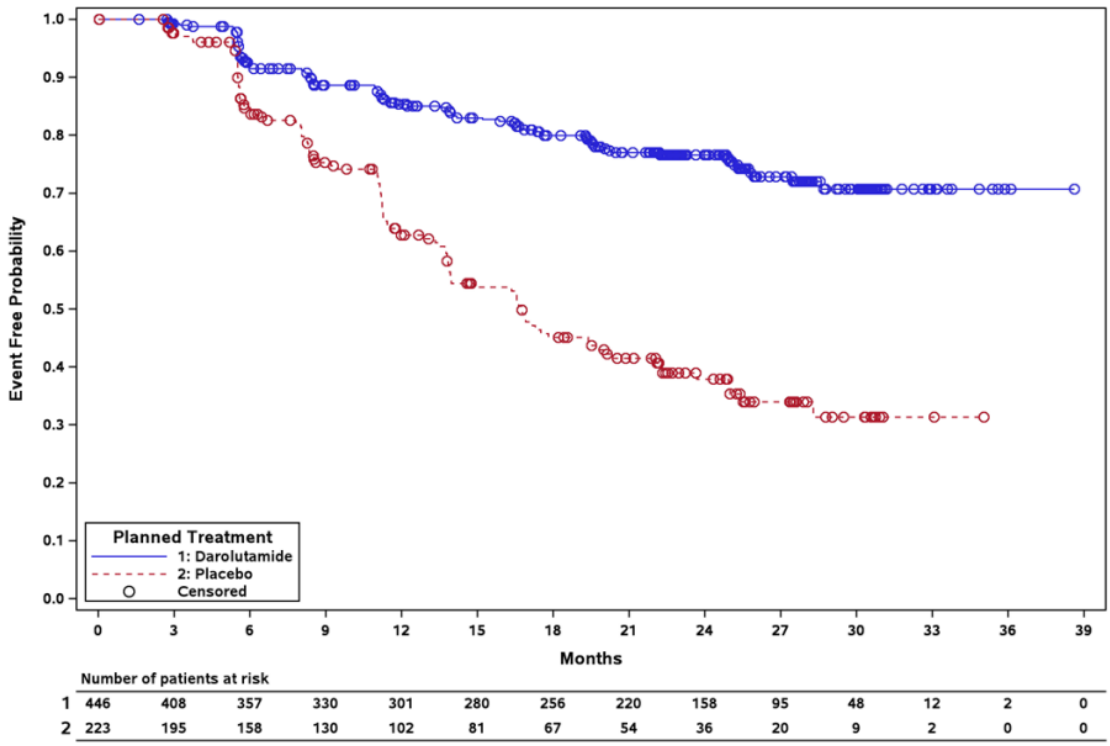
CRPC=Castration-resistant prostate cancer; FAS=Full analysis set
Note: At risk patient counts were calculated as the start of the timepoint.

Time to PSA progression

Baseline PSA values were comparable between the treatment arms (the median values were 21.4 ng/mL in the darolutamide arm and 21.2 ng/mL in the placebo arm; Table 3–4).

A smaller percentage of participants in the darolutamide arm (20.9%) than in the placebo arm (48.4%) had PSA progression based on central PSA assessment. The Kaplan-Meier curves are presented in Figure 6.

Figure 7 Kaplan-Meier curves of time to PSA progression (FAS)



FAS=Full analysis set; PSA=Prostate-specific antigen
Note: At risk patient counts were calculated as the start of the timepoint.

PSA undetectable rate

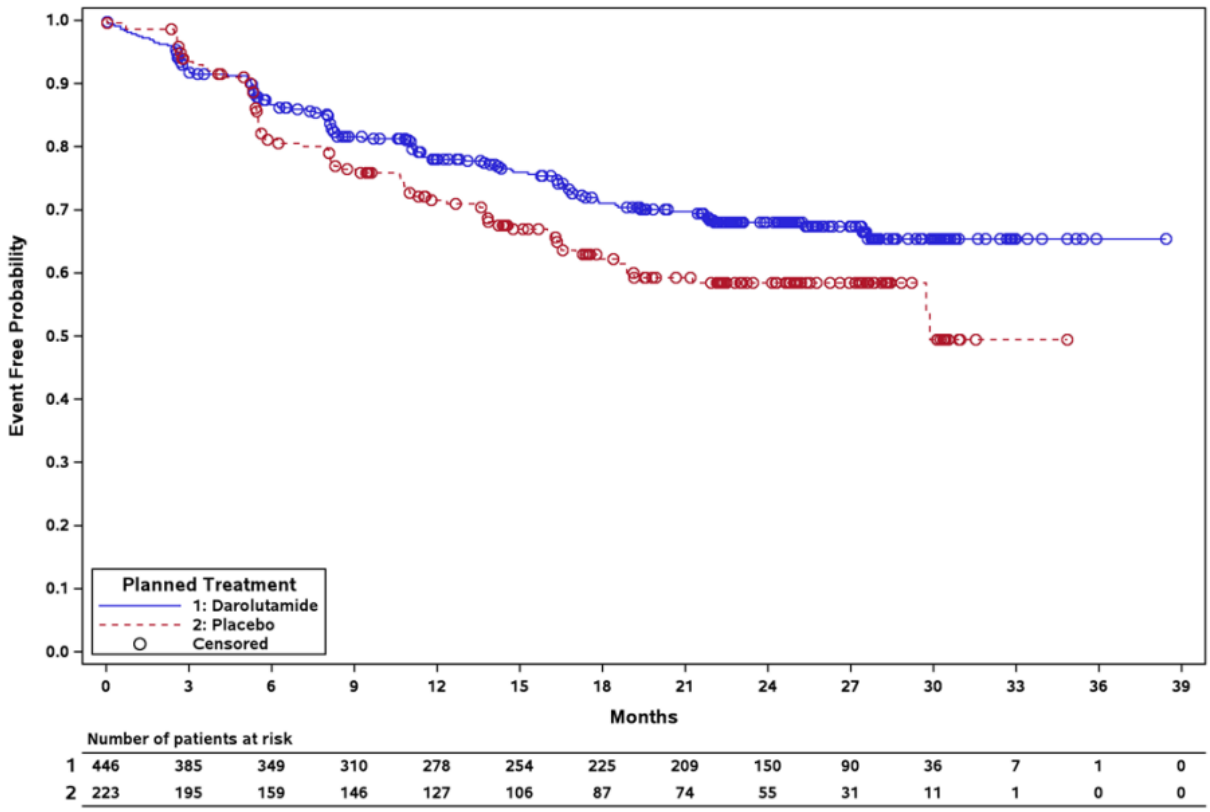
Among participants with detectable PSA values of ≥0.2 ng/mL at baseline (425 participants in the darolutamide arm and 211 participants in the placebo arm), a higher percentage of participants in the darolutamide arm (62.6%) than in the placebo arm (18.5%) reached undetectable PSA values of <0.2 ng/mL at any timepoint during the period between randomization and 30 days after the last dose of the study drug or the start of new anti-cancer therapy, whichever occurred earlier.

Time to pain progression

Pain progression was assessed separately using Q3 of the BPI-SF questionnaire and/or initiation short- or long-acting opioid use for malignant disease for ≥7 consecutive days after randomization. There were 27.8% of participants in the darolutamide arm and 35.4% in the placebo arm with pain progression.

The Kaplan-Meier curves are presented in Figure 7

Figure 8 Kaplan-Meier curves of time to pain progression in ARANOTE (FAS)



FAS=Full analysis set
Note: At risk patient counts were calculated as the start of the timepoint.

Sensitivity analyses of time to pain progression (based on a minimum of 2, 3 or 4 daily reports, i.e. Q3 must be answered within 7 days prior to reporting time point) showed consistent results with the results of the main analysis. Each analysis showed a delay in time to pain progression for participants in the darolutamide arm over the placebo arm.

Other prespecified efficacy endpoints

The results of the other prespecified efficacy endpoints are showed in Table 24 below. Note that the other prespecified endpoints were not formally tested for statistical significance. Nominal p-values are provided for exploratory and descriptive purposes only.

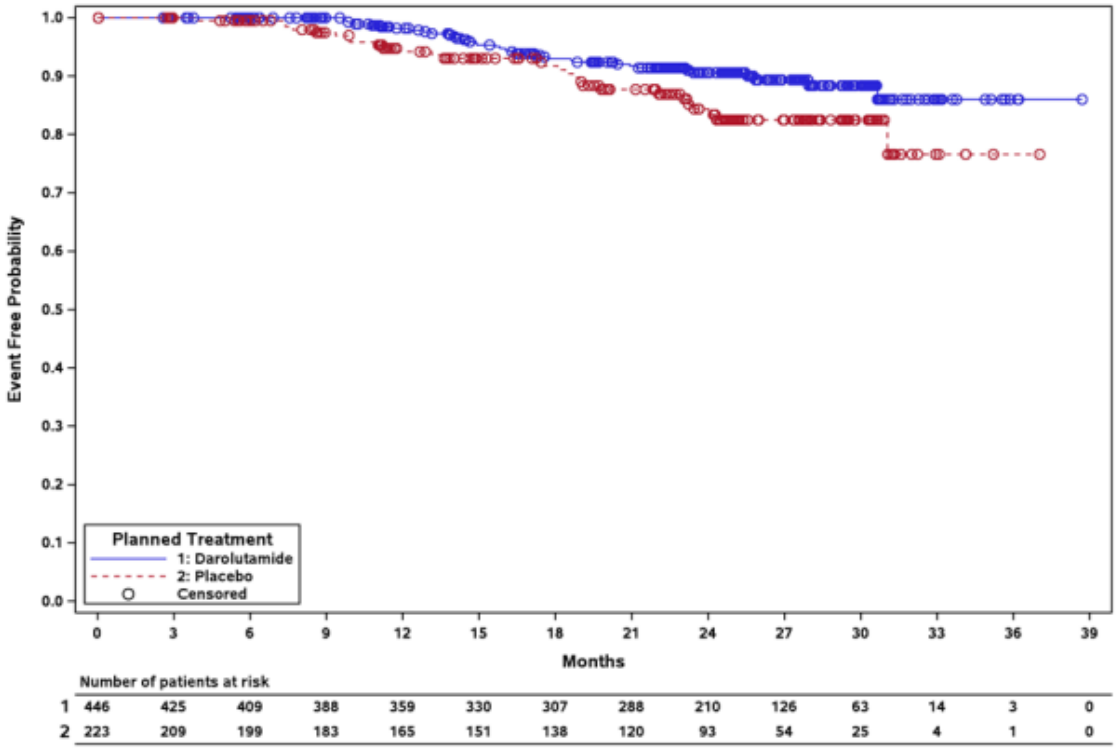
Progression-free survival 2 (PFS 2)

Table 23 PFS 2 (FAS)

	Darolutamide N=446	Placebo N=223
Number (%) of participants with event	36 (8.1)	28 (12.6)
Number (%) of participants censored	410 (91.9)	195 (87.4)
PFS2 (months)		
Median [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03** - 38.7**)	(0.03** - 37.0**)
Range without censored values	(9.7 - 30.7)	(4.0 - 31.0)
Hazard ratio: (darolutamide vs. placebo) [95% CI][a]	0.590 [0.360; 0.968]	
One-sided p-value from stratified log-rank test (IWRS)	0.0173	

A=Value cannot be estimated due to censored data; CI=Confidence interval; FAS=Full analysis set; IWRS=Interactive web response system; N=total number of participants (100%); PFS2=Progression-free survival 2
**Censored observation.
a: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and 95% CI were based on Cox Regression Model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
Note: Median, percentile, and other 95% CIs were computed using Kaplan-Meier estimates.

Figure 9 Kaplan-Meier curves of PFS 2



FAS=Full analysis set
At-risk participant counts were calculated as at the start of the timepoint.

Time to symptomatic skeletal event (TSSE)

Table 24 Time to symptomatic skeletal event (FAS)

	Darolutamide N=446	Placebo N=223
Number (%) of participants with event	28 (6.3)	16 (7.2)
External beam radiation therapy to relieve skeletal symptoms	15 (53.6)	13 (81.3)
New symptomatic pathologic bone fracture	5 (17.9)	1 (6.3)
Tumor-related orthopedic surgical intervention	1 (3.6)	1 (6.3)
Spinal cord compression	7 (25.0)	1 (6.3)
Number (%) of participants censored	418 (93.7)	207 (92.8)
Time to symptomatic skeletal event (months)		
Median [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03** - 38.6**)	(0.03** - 35.1**)
Hazard ratio: (darolutamide vs. placebo) [95% CI][a]	0.826 [0.447; 1.528]	
One-sided p-value from stratified log-rank test (IWRS)	0.2708	

A=Value cannot be estimated due to censored data; CI=Confidence interval; FAS=Full analysis set; IWRS=Interactive web response system; N=Total number of participants (100%); SSE=Symptomatic skeletal event

**Censored observation.

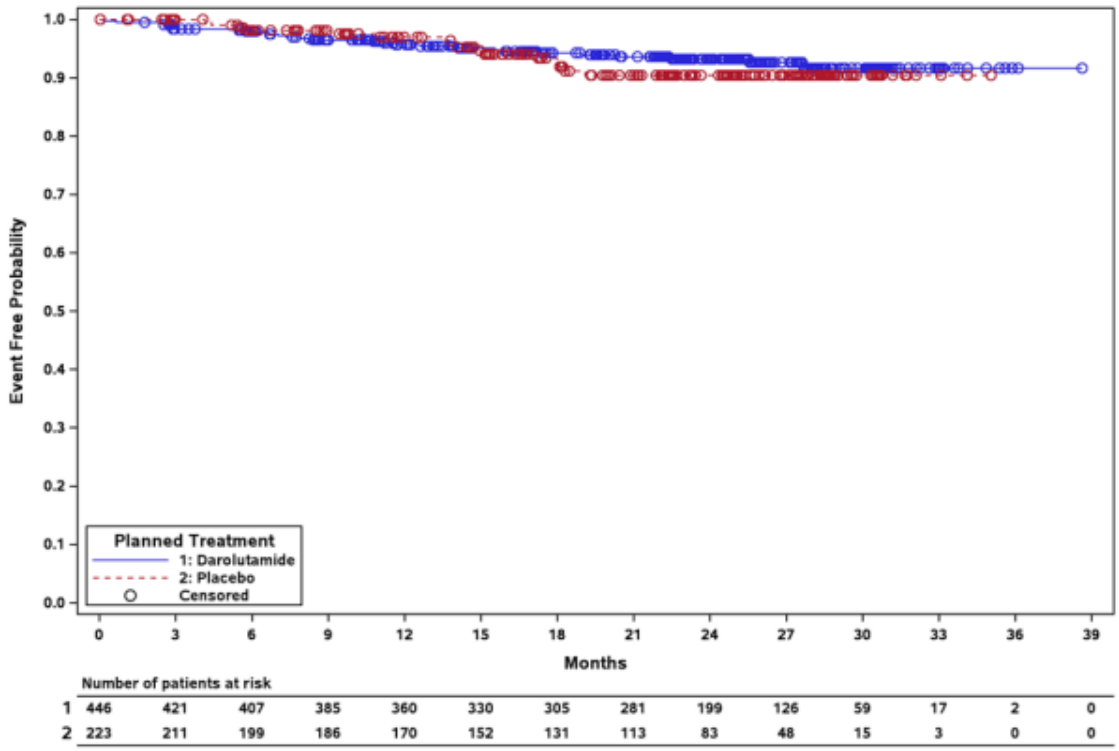
a: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).

Notes: The denominator is the total number of participants with SSE.

Participants with multiple events were only counted for the category in which the first event occurred. If multiple SSE (component events) occurred on the same date for 1 participant, the participant was only counted into 1 category in the order of: spinal cord compression > bone fracture > orthopedic surgery > external beam radiation therapy.

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

Figure 10 Kaplan-Meier curves of TSSE (FAS)



FAS=Full analysis set

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

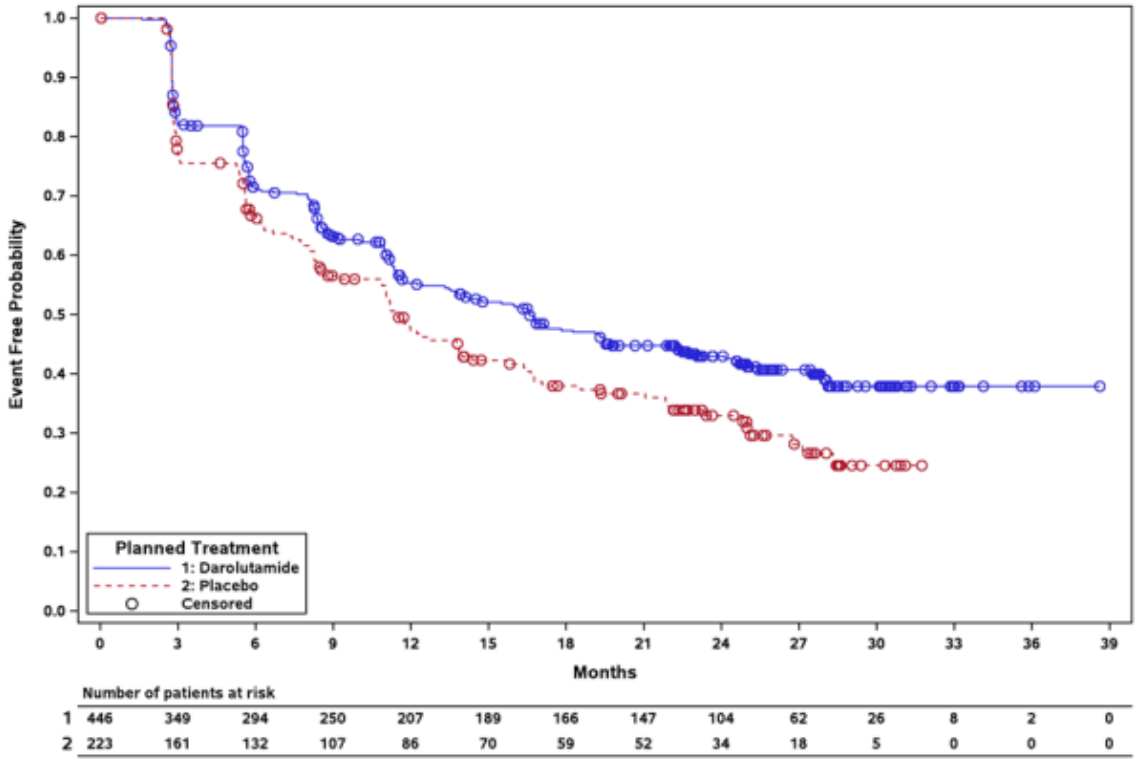
Time to deterioration in FACT-P total score and subscale scores

Table 25 Time to deterioration in FACT-P total score (FAS)

	Darolutamide N=446	Placebo N=223
Number (%) of participants with event	236 (52.9)	136 (61.0)
Number (%) of participants censored	210 (47.1)	87 (39.0)
Time to deterioration in FACT-P total score (months)		
Median [95% CI]	16.6 [12.5; 19.5]	11.5 [8.7; 14.0]
Range (including censored values)	(0.03** - 38.6**)	(0.03** - 31.7**)
Hazard ratio: (darolutamide vs. placebo) [95% CI][a]	0.756 [0.612; 0.935]	
One-sided p-value from stratified log-rank test (IWRS)	0.0045	

CI=Confidence interval; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FAS=Full analysis set; IWRS=Interactive web response system; N=Total number of participants (100%)
**Censored observation.
a: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
Note: Median, percentile, and other 95% CIs were computed using Kaplan-Meier estimates.

Figure 11 Kaplan-Meier curves of Time to deterioration in FACT-P total score (FAS)



FACT-P=Functional Assessment of Cancer Therapy-Prostate; FAS=Full analysis set
At-risk participant counts were calculated as at the start of the timepoint.

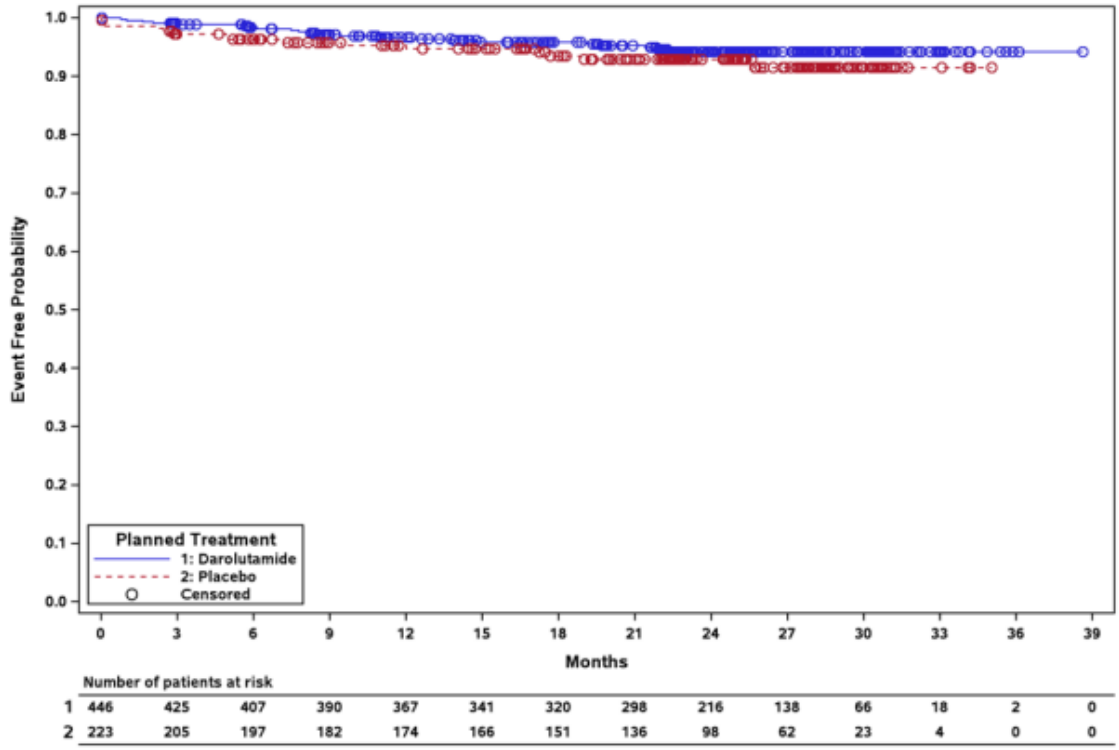
Time to first prostate cancer-related invasive procedures

Table 26 Time to first prostate cancer-related invasive procedures (FAS)

	Darolutamide N=446	Placebo N=223
Number (%) of participants with event	22 (4.9)	15 (6.7)
Number (%) of participants censored	424 (95.1)	208 (93.3)
Time to first prostate cancer-related invasive procedures (months)		
Median [95% CI]	A [A; A]	A [A; A]
Range (including censored values)	(0.03** - 38.6**)	(0.03 - 35.1**)
Hazard ratio: (darolutamide vs. placebo) [95% CI][a]	0.689 [0.357; 1.328]	
One-sided p-value from stratified log-rank test (IWRS)	0.1317	

A=Value cannot be estimated due to censored data; CI=Confidence interval; FAS=Full analysis set; IWRS=Interactive web response system; N=Total number of participants (100%)
**Censored observation.
a: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and 95% CI were based on a Cox Regression Model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
Note: Median, percentile, and other 95% CIs were computed using Kaplan-Meier estimates.

Figure 12 Kaplan-Meier curves of Time to first prostate cancer-related invasive procedures (FAS)



FAS=Full analysis set
At-risk participant counts were calculated as at the start of the timepoint.

Other variables

Patient reported outcomes

The QoL of participants during the study was evaluated using the FACT-P and the BPI-SF questionnaires. QoL and PRO data were mainly based on paper PROs. The compliance for completing both questionnaires was generally comparable and high (≥95% of participants to whom a questionnaire was provided) between the treatment arms throughout the treatment period).

FACT-P questionnaire – total and subscale scores

At baseline, the FACT-P total score and the PWB, SWB, EWB, FWB, and PCS subscale scores were similar between the treatment arms:

• Changes in the mean values from baseline for the FACT-P total score and the subscale scores were similar in both treatment arms, and there were no clinically meaningful differences between the treatment arms up to Visit 12.
• The results of the ANCOVA analysis of time-adjusted AUC for the FACT-P total and subscale scores favoured the darolutamide arm (higher scores represent better QoL), but these were not clinically meaningful, as the differences in the mean values of least squares between the treatment arms did not meet the pre-specified thresholds.
The results suggest that QoL as measured by the FACT-P was maintained while on treatment.

BPI-SF questionnaire – pain assessment

The BPI-SF questionnaire was used to assess clinical pain. Results from Q3, regarding "worst pain in 24 hours" were used for the analysis of time to pain progression as a secondary efficacy endpoint. At baseline, the BPI-SF pain interference and pain severity scores were similar between the treatment arms:
• Changes in the mean values from baseline for the pain severity score and pain interference score were similar in both treatment arms, and there were no clinically meaningful differences between the treatment arms up to Visit 12.
• The results of the ANCOVA analysis of time-adjusted AUC for the pain severity and pain interference scores favoured the darolutamide arm (lower scores represent less pain) but were not clinically meaningful, as the differences in the mean values of least squares between the treatment arms did not meet the pre-specified thresholds. The results suggest that QoL as measured by pain levels was maintained while on treatment.

Ancillary analyses

Sensitivity analyses of rPFS

Table 27 Sensitivity analyses of rPFS (FAS)

Sensitivity analysis		Hazard ratio [a]: Daro vs. Placebo [95% CI]	One-sided p-value from log-rank test
Analysis 1	Considering the impact of all deaths at any time prior to the database cut-off. All deaths from any cause at any time prior to the database cut-off date, regardless of the censoring rules, were included in the rPFS calculation, unless rPD was documented.	0.554 [0.432; 0.710]	<0.0001
Analysis 2	Based on investigator radiological assessment.[b]	0.555 [0.422; 0.730]	<0.0001
Analysis 3	Without stratification: using an unstratified log-rank test and unstratified Cox model.	0.540 [0.413; 0.705]	<0.0001
Analysis 4	Considering the additional primary malignancy (except basal cell carcinoma) diagnosed prior to radiological progression or death, which will be censored at the date of last adequate tumor assessment before or on the diagnosis of additional primary malignancy.	0.538 [0.411; 0.706]	<0.0001
Analysis 5	Without considering the censoring rule of radiological progression/death occurring later than (24+1) weeks of last adequate scan.	0.539 [0.415; 0.701]	<0.0001
Analysis 6	Considering the impact of rPD by BICR documented between the scheduled scans as per protocol (every 12 weeks).[c]	0.548 [0.428; 0.702]	<0.0001

BICR=Blinded independent central review; CI=Confidence interval; Daro=Darolutamide; FAS=Full analysis set; rPD=Radiological disease progression; rPFS=Radiological progression-free survival; SAP=Statistical analysis plan

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

b: Participants with a baseline superscan based on investigator review were censored at the date of randomization.

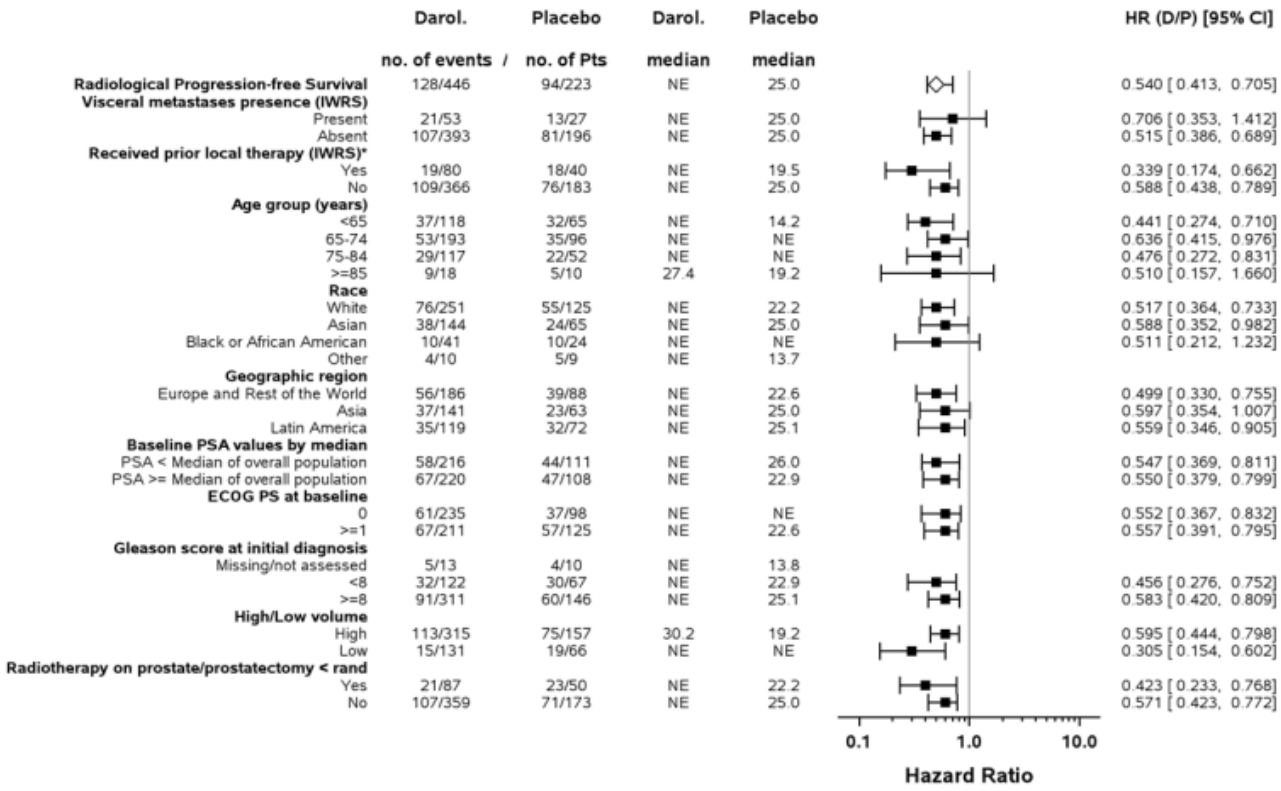
c: For a tumor assessment within the scheduled visit time interval (every 12±1 weeks from randomization), the actual tumor assessment date was used for rPFS. For a tumor assessment outside of the scheduled visit time interval, a tumor assessment date of rPD was moved forward to the date of next scheduled visit; a tumor assessment date of non-rPD was moved backward to the closest prior scheduled visit. rPFS was the time from randomization to rPD, death, withdrawn informed consent, or the database cut-off, whichever came first.

Subgroup analysis of rPFS

Regional subgroup efficacy analysis for rPFS showed a consistent benefit for participants with mHSPC receiving darolutamide across geographic regions

- Europe/ROW HR=0.499 (95% CI: [0.330; 0.755]) Darolutamide N=186, n with event=56 Placebo: N=88, n with event=39
- Asia HR=0.597 (95% CI: [0.354; 1.007]) Darolutamide N=141, n with event=37 Placebo: N=63, n with event=23
- Latin America HR=0.559 (95% CI: [0.346; 0.905]) Darolutamide N=119, n with event=35 Placebo: N=72, n with event=32

Figure 13 Forest Plot of subgroup analysis: rPFS (FAS)



BICR=Blinded independent central review; CI=Confidence interval; D/Darol.=Darolutamide; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FAS=Full analysis set; HR=Hazard ratio; IWRS=Interactive web response system; NE=Value cannot be estimated due to censored data; no.=Number; P=Placebo; PSA= Prostate-specific antigen; Pts=Participants; rPFS=Radiological progression-free survival

Notes:

Progression of disease was based on data from BICR

HR <1 indicates superiority of darolutamide over placebo.

HRs and CIs were obtained from univariate analysis using Cox regression (unstratified).

Median was computed using Kaplan-Meier estimates.

HR estimates with 95% CIs were calculated if ≥10 total events were observed within the subgroup across the treatment arms.

*Prior local therapy (IWRS) included other procedures (e.g. orchiectomy, catheterization).

Summary of main study

Title: A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) vs. placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC)		
Study identifier	Internal study number: 21140 Study name: ARANOTE EudraCT number: 2020–003093–48 EU CT number: 2022–502244–12–00 ClinicalTrials.gov identifier: NCT04736199	
Design	Multinational, randomized (2:1), double-blind, placebo-controlled, Phase 3 efficacy and safety study of oral darolutamide. The patient population included participants with mHSPC. Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by blinded independent central review.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	23 FEB 2021 (FPFV) – 07 JUN 2024 (database cut-off date for the primary completion analysis) not applicable not applicable

Hypothesis	Superiority of darolutamide over placebo in radiological progression-free survival (The primary objective of the study is to determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS, as assessed by BICR for soft tissue and bone metastases)		
Treatments groups	Darolutamide arm		Darolutamide 600 mg (2 tablets of 300 mg) BID with food, equal to a total daily dose of 1200 mg. Concurrently with ADT Duration (overall time under treatment) median (min – max): 24.2 months (0.03–38.8 months) Number randomized: 446 participants [a]
	Placebo arm		Matching placebo BID with food. Concurrently with ADT Duration (overall time under treatment) median (min – max): 17.3 months (0.2–36.7 months) Number randomized: 223 participants [a]
Endpoints and definitions	Primary: Radiological progression-free survival	rPFS	Time from the date of randomization to the date of progressive disease in malignant soft tissue lesions, progressive disease in malignant bone lesions, or death due to any cause, whichever occurred first. The rPFS was assessed by BICR based on RECIST v. 1.1 criteria for malignant soft tissue lesions (Eisenhauer et al. 2009) and PCWG3 criteria for malignant bone lesions (Scher et al. 2016).
	Secondary [b]: Overall survival	OS	Time from the date of randomization to the date of death from any cause.
	Secondary: Time to initiation of subsequent anticancer therapy	Time to 1st subsequent therapy	Time from the date of randomization to the date of initiation of first subsequent anticancer therapy for prostate cancer.
	Secondary: Time to castration-resistant prostate cancer	Time to CRPC	Time from randomization to the date of the following events, whichever came first: occurrence of PSA progression, radiological progression by malignant soft tissue lesions, radiological progression by bone lesions, or occurrence of SSE.
	Secondary: Time to prostate-specific antigen progression	Time to PSA progression	Time from the date of randomization to the date of first PSA progression.
	Secondary: Prostate-specific antigen undetectable rate	PSA undetectable rate	Percentage of participants with detectable PSA values of $\geqslant$0.2 ng/mL at baseline, which became undetectable with any PSA values <0.2 ng/mL during the period between randomization and 30 days after last dose of study drug or start of new anticancer therapy, whichever occurred earliest.

	Secondary: Time to pain progression	Time to pain progression	Time from the date of randomization to the date of first pain progression. Pain progression was assessed by Question 3 of the BPI-SF questionnaire related to the worst pain in the last 24 hours taken as an average for post-baseline score, or initiation of short or long-acting opioids for malignant disease for ⩾7 consecutive days after randomization. Initiation or change in the use of other non-opioid analgesics was not used in the assessment of pain progression.

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Full Analysis Set (all randomized participants) Primary completion database cut-off date: 07 JUN 2024 Final OS analysis cut-off date: 10 JAN 2025		
Descriptive statistics and estimate variability	Treatment group	Darolutamide arm	Placebo arm
	Number of subject	**446**	**223**
	rPFS Median (months)[c] [95% CI] (months)	A [A, A]	25.0 [19.0, A]
	OS Median (months)[c] [95% CI] (months)	A [A, A]	A [A, A]
Effect estimate per comparison	**rPFS**	Comparison groups	Darolutamide vs. Placebo
		Hazard ratio[e]	0.541
		[95% CI]	[0.413, 0.707]
		p-value[f]	<0.0001
	OS	Comparison groups	Darolutamide vs. Placebo
		Hazard ratio[e]	0.776
		[95% CI]	[0.577, 1.045]
		p-value[f]	0.0473

Notes	A=Value cannot be estimated due to censored data; ADT=Androgen deprivation therapy; BID=Twice daily; BICR=Blinded independent central review; BPI-SF=Brief pain inventory – short form; CI=Confidence interval; CRPC=Castration-resistant prostate cancer; CT=Computed tomography; EudraCT=European Clinical Trials Database; FPFV=First participant's first visit; max=Maximum; mHSPC=Metastatic hormone-sensitive prostate cancer; min=Minimum; MRI=Magnetic resonance imaging; FACT-P= Functional Assessment of Cancer Therapy – Prostate; OS=Overall survival; PSA=Prostate-specific antigen; rPFS=Radiological progression-free survival; SAP=Statistical analysis plan; SSE=Symptomatic skeletal event a: A total of 669 participants were randomized. b: The secondary endpoints were tested with a hierarchical gatekeeping procedure in the following order: OS, time to initiation of subsequent anticancer therapy, time to CRPC, time to PSA progression, PSA undetectable rates, and time to pain progression. As OS did not reach the one-sided alpha significance threshold of 0.0202 (one-sided) for this analysis, the other secondary efficacy endpoints were not formally tested for significance.. c: Median and 95% CIs were computed using Kaplan-Meier estimates. e: A hazard ratio <1 indicates superiority of darolutamide over placebo. The hazard ratio and 95% CIs were based on Cox Regression Model, stratified at randomization by IWRS stratification factors: visceral disease (present vs. absent), prior local therapy (yes vs. no). f: One-sided p-value from stratified log-rank test

Clinical studies in special populations

Table 28 Key demographics and baseline characteristics (FAS)

	Darolutamide N=446	Placebo N=223	Total N=669
Age at screening (years)			
N	446	223	669
Mean (SD)	69.6 (8.8)	69.2 (8.9)	69.5 (8.8)
Median	70.0	70.0	70.0
Min, Max	43, 93	45, 91	43, 93
Age category (years), n (%)			
<65	118 (26.5)	65 (29.1)	183 (27.4)
65–74	193 (43.3)	96 (43.0)	289 (43.2)
75–84	117 (26.2)	52 (23.3)	169 (25.3)
≥85	18 (4.0)	10 (4.5)	28 (4.2)
Geographical region, n (%)			
Europe/ROW	186 (41.7)	88 (39.5)	274 (41.0)
Asia	141 (31.6)	63 (28.3)	204 (30.5)
Latin America	119 (26.7)	72 (32.3)	191 (28.6)
Race, n (%)			
White	251 (56.3)	125 (56.1)	376 (56.2)
Black or African American	41 (9.2)	24 (10.8)	65 (9.7)
Asian	144 (32.3)	65 (29.1)	209 (31.2)
Other[a]	10 (2.2)	9 (4.0)	19 (2.8)
Ethnicity, n (%)			
Hispanic or Latino	104 (23.3)	58 (26.0)	162 (24.2)
Not Hispanic or Latino	334 (74.9)	157 (70.4)	491 (73.4)
Not reported	8 (1.8)	8 (3.6)	16 (2.4)

	Darolutamide N=446	Placebo N=223	Total N=669
Body mass index (kg/m^2)			
N	436	221	657
Mean (SD)	25.873 (4.583)	26.191 (4.612)	25.980 (4.592)
Median	25.310	25.800	25.420
Min, Max	15.06, 50.33	14.43, 45.75	14.43, 50.33
Missing	10	2	12

FAS=Full analysis set; Max=Maximum; Min=Minimum; N=Total number of participants (100%); n=Number of participants within category; ROW=Rest of the World; SD=Standard deviation
a: Race 'Other' includes “American Indian or Alaska Native”, “Native Hawaiian or other Pacific Islander”, and “Multiple”.
Note: Data collection for race and ethnicity was not allowed in some countries/regions due to local regulations.

Supportive study(ies)

Study 17777 (ARASENS) was a phase III, multinational, randomized, double-blind, placebo controlled study to assess darolutamide versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

Efficacy and safety were previously established with procedure EMEA/H/C/004790/II/0009.

A total of 1,306 patients were randomly assigned (1:1) to oral darolutamide 600 mg twice daily or matched placebo, in combination with ADT and docetaxel.

Summary of Efficacy and conclusion for the ARASENS study:
Darolutamide with ADT and docetaxel demonstrated statistically significant and clinically meaningful improvements in overall survival (primary endpoint) compared to placebo with ADT and docetaxel in the study 17777 (ARASENS) in patients with mHSPC.
• HR of 0.68 (95% CI: [0.57; 0.801]; p<0.001) representing a 32.5% reduction in the risk of metastases or death.
• The median OS was NE (95% CI: [NE-NE]) in the darolutamide arm compared to 48.9 months (95% CI: [44.4; NE]) in the placebo arm.
Other secondary and exploratory endpoints of the ARASENS study showed a clinically relevant benefit of darolutamide treatment as well: time to CRPC (HR 0.36; 95% CI: 0.30–0.42; p 0.001), time to pain progression (HR 0.79; 95% CI: 0.66–0.95; p=0.01), SSE-FS (HR 0.609; 95% CI: 0.516-0.718; p<0.0001), time to first SSE (HR 0.712; 95% CI: 0.539-0.940; p=0.0081), time to initiation of subsequent systemic antineoplastic therapy (HR 0.388; 95% CI: 0.328-0.458; p< 0.0001) and time to PSA progression (HR 0.26; 95% CI: 0.21–0.31 p<0.0001).

2.4.3. Discussion on clinical efficacy

The MAH for darolutamide requested to extend the indication as follows:

Nubeqa, for the treatment of adult men, with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.

Design and conduct of clinical studies

ARANOTE is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS in participants with mHSPC.

Scientific Advice from CHMP was received in September 2020 (EMA/CHMP/SAWP/470034/2020), addressing the proposed design of ARANOTE study.

In the Scientific Advice, the CHMP recommended to include only patients ineligible for chemotherapy for the primary analysis nevertheless the MAH did not follow the recommendation of CHMP and expanded the initially proposed patient population "mHSPC patients for whom chemotherapy is not planned" to "mHSPC patients" to anticipate the benefit of darolutamide in mHSPC, as it was demonstrated in ARASENS, in mHSPC in combination with docetaxel and ADT.

According to the MAH, the definition of patients eligible to chemotherapy can largely vary because of the multiple objective and subjective criteria considered, including patient's clinical condition and/or patient's preference (Gillessen et al. 2025). Such justification can be accepted to support the administration of darolutamide in patients potentially eligible to chemotherapy, although the study could have been amended with the evolution of SOC.

The CHMP also recommended changing the comparator arm of ARANOTE from ADT plus placebo to ADT plus treatment of investigator's choice since the CHMP no longer considered ADT alone as a standard of care for patients de novo metastatic at diagnosis with a high volume/high risk mHSPC, notably in the EU (NCCN 2025, ESMO 2023).

The justification of the MAH that ADT monotherapy remains a common option for patients with mHSPC with 38% of mHSPC patients still treated with ADT alone (Goebell et al. 2024) in the EU countries is problematic. ADT alone is no longer considered as SoC in patients with mHSPC given the availability of therapies such as docetaxel, abiraterone acetate with prednisolone, enzalutamide and apalutamide, all of which are approved in combination with ADT.

All these treatments are SoC in combination with ADT and have previously demonstrated a survival benefit when compared to ADT alone in patients with mHSPC (ESMO recommendations 2023).

During the Scientific Advice received the CHMP was in favour of a randomised comparison to investigator's choice and ADT (instead of Placebo and ADT) and alternative comparators (e.g. apalutamide or abiraterone acetate plus ADT). Indeed, if a single reference regimen could not be defined, investigator's best choice would have been an option as for EMA guideline on the clinical evaluation of anticancer medicinal products - EMA/CHMP/205/95 Rev.6). CHMP encouraged the Applicant to return for follow up scientific advice to allow evaluation of any revised proposals, should the study design be modified to offer all patients an appropriate treatment comparator (SA dated 17 September 2020) nevertheless this important recommendation was not followed by MAH.

The CHMP pointed out also to an additional concern on the stratification's factors. The presence of visceral metastases, known as poor prognosis criteria and the presence of prior local therapy are used to balance the targeted population (mHSPC) between randomization arms. These stratified randomization factors are acceptable notably as important prognostic covariates and are used as part of covariates for prespecified subgroups analysis (EMA/CHMP/205/95 Rev.6). The CHMP recommendation to stratify by patient's ineligibility vs unwillingness to receive chemotherapy was not followed.

Study participants:

ARANOTE included males ≥18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate that was documented to be metastatic by conventional imaging. Metastatic disease was defined as either malignant lesions in bone scan or measurable lymph nodes above the aortic bifurcation or soft tissue/visceral lesions according to RECIST version 1.1. Lymph nodes were measurable if the short axis diameter is ≥15 mm, soft tissue/visceral lesions were measurable if the long axis diameter is ≥10 mm. Regional lymph node metastases only (N1, below the aortic bifurcation) were not considered as metastases eligible for the study. Only participants with non-regional lymph node metastases (M1a)

and/or bone metastases (M1b) and/or other sites of metastases with or without bone disease (M1c), assessed according to National Comprehensive Cancer Network (NCCN) classification, were eligible.

Participants must have started ADT (LHRH agonist/antagonist or orchiectomy) no longer than 12 weeks before randomization; for participants receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 14 days prior to randomization is recommended in ARANOTE and extend to 4 weeks prior to randomization in ARASENS study. Patients must have ECOG PS of 0, 1 or 2 in ARANOTE while restricted to ECOG of 0 or 1 in ARASENS.

Based on the positive results with benefit of darolutamide on OS in ARASENS study (mHSPC setting), the MAH anticipated the effect and enlarged the targeted population to "mHSPC" in ARANOTE study. This aimed to demonstrate the efficacy of darolutamide without docetaxel in mHSPC in line with the results previously seen for abiraterone acetate with prednisolone, enzalutamide, and apalutamide, approved in combination with ADT in the same indication.

Treatments:

The selected dose of darolutamide for this study is the recommended dose approved in the SmPC, sections 4.2 and 5.2, which is agreed. Dose modifications are acceptable.

Objectives/endpoints:

The primary endpoint rPFS assessed by BICR is acceptable, although overall survival would have been preferable as a robust endpoint (without bias of interpretations) and to compare with the available therapies combined with ADT that have proven efficacy on OS in patients with mHSPC.

The secondary endpoints are relevant, including OS as the key secondary endpoint, and some exploratory endpoints should be considered at least as secondary endpoints: notably PFS2 as an overall efficacy endpoint clinically relevant and time to deterioration in FACT-P total score and time to symptomatic skeletal events (SSE) to estimate the QoL benefit of darolutamide vs control arm as recommended by ESMO in methodological and reporting standards for QoL (S.F. Oosting et all. 2023).

Statistical methods:

Regarding statistical analyses, as mentioned in the CHMP Scientific Advice (EMA/CHMP/SAWP/470034/2020), demonstration of superiority on the primary endpoint is considered as a minimum requirement in a randomized controlled placebo trial in mHSPC setting, with any assessment taking into account relevant efficacy already established in similar settings with available comparators.

For the calculation of sample size, the targeted treatment effect on rPFS (HR 0.625), one-sided alpha of 0.025 and power of 90% were considered acceptable. The use of randomization ratio 2:1 was agreed. However, lower HR of PFS in mHSPC with abiraterone, prednisone plus ADT (HR 0.47), apalutamide (HR 0.48) and enzalutamide (HR 0.40) compared to the same comparator arm (ADT plus placebo) have been recently published (ESMO 2023). While enzalutamide was assessed first in the treatment of mHSPC, the expected HR of 0.625 in ARANOTE seems moderate in terms of efficacy in favour of darolutamide.

The efficacy analyses were performed in the Full Analysis Set, including all participants who were randomized, in line with the intent-to-treat principle. The choice of primary and secondary estimands corresponding to clinical questions of interest (rPFS, OS respectively) is acceptable and encompasses appropriate dimensions (treatments, population and endpoints as variables). The censoring rules are described and supported. It was planned to perform analysis of primary endpoint when approximately 214 events of rPFS were observed in 555 patients (39% of the total expected events) but the analysis of primary endpoint was finally performed in 222 events of rPFS in 669 patients (33.2%). Following the CHMP warning about the low level of maturity which could over-represent the early progressers and give a wrong estimate of efficacy in the whole sought indication and may not allow for adequate assessment of benefit-risk in relevant subgroups.

Otherwise, rPFS was analyzed with log-rank test and Cox regression proportional hazard model, stratified by the same factor as used for randomization. The analysis of secondary endpoints was performed also in the FAS with Time–to–event endpoints analysed using same method as the primary efficacy variable. Only overall survival will be tested at the final analysis time point, when the open-label phase is ended. The statistical methods for analysing primary and secondary endpoints (Kaplan-Meier analyses, stratified log-rank test and Cox model) are standard and adequate for these time to event variables.

Subjects disposition:

The study, conducted in 15 countries/regions, started enrolling participants on 23 February 2021 and was completed on 09 August 2022. The primary completion of the study, with 222 rPFS events, was achieved on 07 June 2024 (data cut-off).

At the time of the data cut-off, the study drug was permanently discontinued in a lower percentage of participants in the darolutamide arm than in the placebo arm (45.5% vs. 71.7%, respectively) and the main reason of drug discontinuation is disease progression in favour of benefit of darolutamide.

Study conduct:

An open-label phase was added in the protocol Amendment 1 (Global), version 2 dated 28 Jun 2022, to offer the opportunity to participants who were on the study treatment (darolutamide or placebo) to receive darolutamide, at the discretion of the investigator. The cross-over is suitable notably to comparator arm potentially deprived of appropriate therapy.

The futility analysis was removed in the Amendment 1 (Global), version 2 dated 28 Jun 2022, as it was considered not needed in light of additional data from ARASENS study, where darolutamide in combination with docetaxel and ADT demonstrated benefit in mHSPC setting over placebo in combination with docetaxel and ADT. The deletion of the futility analysis is questionable given that the comparator arm in ARANOTE study was not the SOC and could have been carefully monitor by the DMC for efficacy and futility analysis (not done).

More than half of the protocol deviations are related to study procedures including screening (screen failures) and study assessment. There is a trend for more study procedure deviations in placebo arm (not statistically significant). Protocol deviations occurred with similar frequency between treatments arms.

Baseline characteristics:

Key demographic and baseline characteristics are well-balanced between the darolutamide and placebo arms. The median age was 70.0 years and the majority of participants were White (56.2%), followed by Asian (31.2%), Black or African American (9.7%), and other (2.8%). Most of participants present extend of metastatic disease at study entry of M1b (77.0%) with bone extension, without visceral metastases (88.0%) and no prior local therapy (82.1%). The stage of prostate cancer at initial diagnosis was mainly IVB and *de novo* (72.5% both). All patients are in Stage IVB (100%) at the study entry with mainly high volume (70.6%). The baseline ECOG PS was 0, 1 or 2 for 49.8%, 47.2% and 3.0% of the participants, respectively.

Prior anticancer therapy and procedures were well balanced between darolutamide and placebo arm at the study entry. All participants received concomitant ADT, except for 1 participant who received one dose of ADT prior to the start of study and did not receive any further doses of ADT. The majority of participants in both treatment arms (82.7% in the darolutamide arm and 81.6% in the placebo arm) had unresected tumour.

As of the cut-off date, 53.8% of participants in the darolutamide arm and 28.3% of participants in the placebo arm were ongoing with study treatment. The reasons of study drug discontinuation were previously discussed (notably, the high rate of disease progression in the placebo arm). Fewer participants in the darolutamide arm than in the placebo arm received a subsequent life-prolonging

systemic anticancer medication for prostate cancer: 14.8% in the darolutamide arm vs. 30.5% in the placebo arm.

Efficacy data and additional analyses

Primary endpoints:

Darolutamide met its primary endpoint and demonstrated a statistically significant improvement and consistent benefit in rPFS based on BICR compared to placebo in participants with mHSPC across multiple timepoints. The robustness of rPFS results was confirmed through the sensitivity and subgroups analyses.

- The HR was 0.541 (95% CI: [0.413; 0.707]; one-sided p<0.0001), representing a 45.9% reduction in the risk of radiological progression or death in the darolutamide arm compared to the placebo arm.
- The median rPFS time was not reached in the darolutamide arm and was 25.0 months (95% CI: [19.0; not estimable]) in the placebo arm.
- The rPFS rates at 6, 12, 18, 24, and 30 months were higher in the darolutamide arm compared with the placebo arm, showing a benefit of darolutamide over time.

A consistent rPFS benefit for darolutamide was observed across all prespecified sensitivity analyses and all prespecified subgroups, including race, geographic region, presence of visceral metastases, prior local therapy, stage at initial diagnosis and high and low volume subgroups.

After the primary analysis of rPFS, once the study was unblinded, patients receiving placebo were offered treatment with open-label darolutamide (cross-over option). Among the 63 patients still on placebo treatment at the data cut-off for primary analysis 60 (95%) crossed over to receive darolutamide treatment.

While the study demonstrated that the combination of darolutamide and ADT significantly improved rPFS compared to ADT alone, more evidence was requested during the procedure to confirm the results in mHSPC patients who were eligible for chemotherapy. This is due to the low maturity of rPFS and OS data and the use of a suboptimal comparator, especially since intensified treatment is the standard of care in this context.

In ARANOTE, the maturity of rPFS, based on the primary completion data (final rPFS analysis), was however consistent with ARCHES (enzalutamide) and TITAN (apalutamide) studies, being 33.2% in ARANOTE (222 rPFS events/669 randomized participants), 35% in TITAN and 25% in ARCHES. Moreover, to investigate any potential effect of disproportional representation of early rPFS events on the HR, the MAH provided a weighted log-rank analysis with weights based on censoring probabilities to correct for any potential overrepresentation of early rPFS events. Based on this analysis, the average HR was 0.577, which is similar to the primary rPFS result (HR of 0.541). This indicates that any influence of potential disproportions due to early progressions is negligible.

Secondary endpoints:

Analysis of the key secondary endpoint, OS, did not demonstrate a statistically significant improvement of OS with darolutamide compared to placebo in the interim analysis

- The HR was 0.813 (95% CI: [0.591; 1.118]; one-sided p=0.1007), with 103 (23.1%) deaths in darolutamide arm and 60 (26.9%) deaths in placebo arm.
- The median OS was not reached in either arm for the darolutamide vs. placebo arm in the interim analysis.

However, in the final OS data, provided by the MAH (database cut-off date (10 JAN 2025)), a positive trend in favor of darolutamide was observed with an HR of 0.776 (95% CI: [0.577; 1.045]; one-sided p=0.0473); 185 OS events have occurred: 115 participants in the darolutamide arm and 70 participants

in the placebo arm. The median follow-up time for OS was 31.4 months for the darolutamide arm and 30.5 months for the placebo arm. The subgroup analyses of OS showed also a trend in favor of darolutamide in all prespecified subgroups. The OS analysis was not adjusted for confounding effects of cross-over.

Since OS was not statistically significant at the prespecified alpha significance level of 0.0202 (one-sided) based on 185 OS events observed, the other secondary endpoints were not formally tested for statistical significance according to the hierarchical gatekeeping procedure and results have to be interpreted with caution.

- A benefit in favour of darolutamide was observed for all other secondary endpoints compared with placebo:
    - time to initiation of subsequent anticancer therapy; HR=0.401; 95% CI: [0.288, 0.558]; p<0.0001
    - time to CRPC; HR=0.404; 95% CI: [0.321, 0.508]; p<0.0001
    - time to PSA progression; HR=0.306; 95% CI: [0.231; 0.405]; p<0.0001
    - PSA undetectable rate with a rate difference of 44.3% in favour of darolutamide; p<0.0001
    - time to pain progression; HR=0.721; 95% CI: [0.544; 0.957]; p=0.0115.

A sensitivity analysis of time to CRPC was performed without considering the occurrence of symptomatic skeletal events (SSE) as a CRPC event. SSEs were reported in a low percentage of participants in both treatment arms: 6.3% in the darolutamide arm and 7.2% in the placebo arm (data not shown). The percentage of events in this time to CRPC sensitivity analysis was lower in the darolutamide arm (32.3%) compared with the placebo arm (63.2%). The results support the main analysis of time to CRPC, with an HR of 0.366 (95% CI: [0.290; 0.463]); p<0.0001.

Prespecified efficacy endpoints:

- The benefit of darolutamide was also observed in the other prespecified efficacy endpoints:
    - PFS2; HR=0.590; 95% CI: [0.360; 0.968]; p=0.0173
    - time to SSE; HR=0.826; 95% CI: [0.447; 1.528]; p=0.2708
    - time to deterioration in FACT-P total score; HR=0.756; 95% CI: [0.612; 0.935]; p=0.0045
    - time to first prostate cancer-related invasive procedure; HR=0.689; 95% CI: [0.357; 1.328]; p=0.1317.
- No clinically meaningful differences in HR QoL were observed between the treatment arms, as measured by the FACT-P and the BPI-SF questionnaires, indicating that QoL was maintained.

The following wording of indication is recommended:

NUBEQA is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (see section 5.1).

2.4.4. Conclusions on the clinical efficacy

The final rPFS analysis of study ARANOTE showed statistically and clinically meaningful improvements with darolutamide plus ADT treatment compared to placebo plus ADT in men with mHSPC. The benefit of darolutamide on rPFS was consistent and supported by subgroups and sensitivity analyses.

The subgroup analyses of OS showed also a trend in favour of darolutamide in all prespecified subgroups.

2.5. Clinical safety

Introduction

The main analyses to support the safety of darolutamide are based on the phase 3 study 21140 (ARANOTE) in men with mHSPC. To further support the safety analyses, the data from ARANOTE and Study 17712 (ARAMIS), were pooled. Supportive results for the long-term safety of darolutamide are provided by study 20321 ROS.

Study 21140 (ARANOTE), a randomized, double-blind, placebo-controlled, phase 3 study of darolutamide in participants with mHSPC, is ongoing. At the time of the primary completion (07 JUN 2024), there were 303 participants still on treatment: 240 receiving darolutamide and 63 receiving placebo.

Study 17712 (ARAMIS), a randomized, double-blind, placebo-controlled, phase 3 efficacy and safety study of darolutamide in participants with nmCRPC at high risk of developing metastatic disease, has been completed. The study was conducted globally, including in the US, Latin America, Europe, and Asia Pacific. The primary completion of the study was reached on 03 SEP 2018. An open-label (OL) part started on 30 OCT 2018. Participants originally assigned to darolutamide continued OL darolutamide treatment (DB+OL period) and 170 participants, who were ongoing in the placebo arm, crossed over to receive OL darolutamide treatment (CO period).

Patient exposure

Table 29 Darolutamide/placebo exposure and dose modification- ARANOTE and ARANOTE+ARAMIS pool (SAF)

		ARANOTE		ARANOTE+ARAMIS	
Parameter		Darolutamide N=445	Placebo N=221	Darolutamide N=1399	Placebo N=775
Overall time under treatment (months)					
Mean (SD)		21.322 (9.162)	17.736 (9.322)	18.232 (9.601)	13.849 (8.954)
Median		24.212	17.346	18.167	11.564
Min, Max		0.03, 38.80	0.23, 36.73	0.03, 44.28	0.07, 40.47
Exposure Categories (months), n (%)					
<1		2 (0.4)	2 (0.9)	19 (1.4)	11 (1.4)
≥1		443 (99.6)	219 (99.1)	1380 (98.6)	764 (98.6)
≥3		432 (97.1)	210 (95.0)	1351 (96.6)	736 (95.0)
≥6		416 (93.5)	191 (86.4)	1276 (91.2)	600 (77.4)
≥12		343 (77.1)	149 (67.4)	923 (66.0)	371 (47.9)
≥24		224 (50.3)	76 (34.4)	444 (31.7)	138 (17.8)
Dose Modifications					
Number of participants with any dose modification, n (%)		99 (22.2)	30 (13.6)	244 (17.4)	84 (10.8)
Number of dose modifications		297	75	516	153
Primary reason for modification [no. (%) of events]					
Adverse event		112/297 (37.7)	22/75 (29.3)	296/516 (57.4)	79/153 (51.6)
Subject error		147/297 (49.5)	45/75 (60.0)	147/516 (28.5)	45/153 (29.4)
Subject decision: Covid-19 pandemic related		15/297 (5.1)	1/75 (1.3)	15/516 (2.9)	1/153 (0.7)
Physician decision: Covid-19 pandemic related		2/297 (0.7)	0	2/516 (0.4)	0
Other		21/297 (7.1)	7/75 (9.3)	56/516 (10.9)	28/153 (18.3)
Number of dose modifications per participant, n (%)	1	48/99 (48.5)	15/30 (50.0)	145/244 (59.4)	52/84 (61.9)
	2	21/99 (21.2)	9/30 (30.0)	56/244 (23.0)	21/84 (25.0)
	3	8/99 (8.1)	1/30 (3.3)	13/244 (5.3)	4/84 (4.8)
	4	10/99 (10.1)	3/30 (10.0)	16/244 (6.6)	5/84 (6.0)
	5	5/99 (5.1)	0	6/244 (2.5)	0
	6	2/99 (2.0)	0	2/244 (0.8)	0
	7	0	0	0	0
	8	1/99 (1.0)	1/30 (3.3)	2/244 (0.8)	1/84 (1.2)
	9	1/99 (1.0)	0	1/244 (0.4)	0
	≥10	3/99 (3.0)	1/30 (3.3)	3/244 (1.2)	1/84 (1.2)
Dose interruptions					
Number of participants with any dose interruption, n (%)		92 (20.7)	27 (12.2)	207 (14.8)	74 (9.5)
Number of dose interruptions		265	67	401	122
Dose reductions					
Number of participants with any dose reduction, n (%)		25 (5.6)	8 (3.6)	89 (6.4)	27 (3.5)
Number of dose reductions		32	8	115	31
Dose re-escalations					
Number of participants with any dose re-escalation, n (%)		13 (2.9)	4 (1.8)	57 (4.1)	11 (1.4)
Number of dose re-escalations		14	5	63	13

COVID-19=Coronavirus disease 2019; N=Number of participants; SAF=Safety analysis set

Note: Only modifications after start of treatment and before end of treatment are included.

Modifications include interruptions, reductions, and re-escalation.

Adverse events

Most common TEAEs

Table 30 Most common TEAEs (reported in ≥2 % of participants) in either treatment arm - ARANOTE and ARANOTE+ARAMIS pool (SAF)

	ARANOTE				ARANOTE+ARAMIS			
	Darolutamide N=445		Placebo N=221		Darolutamide N=1399		Placebo N=775	
Preferred term	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Arthralgia	55 (12.4)	7.4	25 (11.3)	8.0	150 (10.7)	7.4	83 (10.7)	9.5
Anaemia	91 (20.4)	12.5	39 (17.6)	12.5	144 (10.3)	7.0	64 (8.3)	7.1
Fatigue	25 (5.6)	3.2	18 (8.1)	5.7	140 (10.0)	6.9	66 (8.5)	7.4
Back pain	43 (9.7)	5.6	23 (10.4)	7.1	126 (9.0)	6.0	72 (9.3)	8.0
Constipation	42 (9.4)	5.5	16 (7.2)	5.0	102 (7.3)	4.8	50 (6.5)	5.5
Hypertension	38 (8.5)	5.0	19 (8.6)	6.0	101 (7.2)	4.8	48 (6.2)	5.3
Urinary tract infection	52 (11.7)	6.8	17 (7.7)	5.3	99 (7.1)	4.7	45 (5.8)	5.0
Pain in extremity	38 (8.5)	5.0	20 (9.0)	6.1	93 (6.6)	4.4	38 (4.9)	4.1
Hot flush	41 (9.2)	5.6	16 (7.2)	5.0	91 (6.5)	4.4	39 (5.0)	4.3
Diarrhoea	15 (3.4)	1.9	7 (3.2)	2.1	81 (5.8)	3.8	38 (4.9)	4.2
Haematuria	22 (4.9)	2.8	10 (4.5)	3.0	63 (4.5)	2.9	37 (4.8)	4.0
Nausea	11 (2.5)	1.4	5 (2.3)	1.5	59 (4.2)	2.8	37 (4.8)	4.0
Oedema peripheral	19 (4.3)	2.4	7 (3.2)	2.1	58 (4.1)	2.7	24 (3.1)	2.6
Aspartate aminotransferase increased	43 (9.7)	5.7	17 (7.7)	5.3	56 (4.0)	2.6	18 (2.3)	1.9
Headache	18 (4.0)	2.3	14 (6.3)	4.3	55 (3.9)	2.6	28 (3.6)	3.1
Insomnia	28 (6.3)	3.6	6 (2.7)	1.8	54 (3.9)	2.5	16 (2.1)	1.7
Asthenia	15 (3.4)	1.9	9 (4.1)	2.7	51 (3.6)	2.4	28 (3.6)	3.0
Cough	21 (4.7)	2.7	7 (3.2)	2.1	50 (3.6)	2.3	18 (2.3)	1.9
Pollakiuria	11 (2.5)	1.4	2 (0.9)	0.6	49 (3.5)	2.3	18 (2.3)	1.9
Weight decreased	14 (3.1)	1.8	6 (2.7)	1.8	48 (3.4)	2.2	18 (2.3)	1.9
Alanine aminotransferase increased	40 (9.0)	5.3	18 (8.1)	5.6	47 (3.4)	2.2	19 (2.5)	2.1
Weight increased	33 (7.4)	4.4	17 (7.7)	5.4	47 (3.4)	2.2	24 (3.1)	2.6
Dizziness	9 (2.0)	1.1	4 (1.8)	1.2	44 (3.1)	2.0	18 (2.3)	1.9
Blood creatinine increased	21 (4.7)	2.7	15 (6.8)	4.7	43 (3.1)	2.0	29 (3.7)	3.1
Bone pain	33 (7.4)	4.2	27 (12.2)	8.4	42 (3.0)	1.9	33 (4.3)	3.6
Decreased appetite	14 (3.1)	1.8	9 (4.1)	2.7	42 (3.0)	1.9	25 (3.2)	2.7
Nasopharyngitis	6 (1.3)	0.8	3 (1.4)	0.9	42 (3.0)	2.0	24 (3.1)	2.6
Fall	5 (1.1)	0.6	2 (0.9)	0.6	41 (2.9)	1.9	25 (3.2)	2.7
Urinary retention	8 (1.8)	1.0	6 (2.7)	1.8	41 (2.9)	1.9	42 (5.4)	4.6
Pyrexia	20 (4.5)	2.5	7 (3.2)	2.1	39 (2.8)	1.8	12 (1.5)	1.3
Pneumonia	16 (3.6)	2.0	2 (0.9)	0.6	38 (2.7)	1.7	13 (1.7)	1.4
Upper respiratory tract infection	12 (2.7)	1.5	2 (0.9)	0.6	37 (2.6)	1.7	11 (1.4)	1.2
Hyperglycaemia	27 (6.1)	3.5	8 (3.6)	2.4	36 (2.6)	1.7	11 (1.4)	1.2
Dysuria	14 (3.1)	1.8	7 (3.2)	2.1	35 (2.5)	1.6	34 (4.4)	3.7
Influenza	6 (1.3)	0.8	1 (0.5)	0.3	33 (2.4)	1.5	10 (1.3)	1.1
Abdominal pain	8 (1.8)	1.0	5 (2.3)	1.5	32 (2.3)	1.5	17 (2.2)	1.8
COVID-19	32 (7.2)	4.2	15 (6.8)	4.7	32 (2.3)	1.5	15 (1.9)	1.6
Blood alkaline phosphatase increased	30 (6.7)	3.8	13 (5.9)	3.9	31 (2.2)	1.4	16 (2.1)	1.7
Blood bilirubin increased	19 (4.3)	2.4	2 (0.9)	0.6	31 (2.2)	1.4	2 (0.3)	0.2
Dyspnoea	7 (1.6)	0.9	4 (1.8)	1.2	31 (2.2)	1.4	19 (2.5)	2.0
Atrial fibrillation	6 (1.3)	0.8	2 (0.9)	0.6	28 (2.0)	1.3	10 (1.3)	1.1
Rash	11 (2.5)	1.4	5 (2.3)	1.5	28 (2.0)	1.3	9 (1.2)	1.0
Hyperkalaemia	8 (1.8)	1.0	8 (3.6)	2.4	24 (1.7)	1.1	17 (2.2)	1.8
Pruritus	8 (1.8)	1.0	5 (2.3)	1.5	24 (1.7)	1.1	16 (2.1)	1.7
Pelvic pain	8 (1.8)	1.0	5 (2.3)	1.5	20 (1.4)	0.9	17 (2.2)	1.8
Hypokalaemia	9 (2.0)	1.1	3 (1.4)	0.9	18 (1.3)	0.8	5 (0.6)	0.5
Hyponatraemia	11 (2.5)	1.4	6 (2.7)	1.8	18 (1.3)	0.8	8 (1.0)	0.9
Pain	12 (2.7)	1.5	5 (2.3)	1.5	17 (1.2)	0.8	12 (1.5)	1.3
Platelet count decreased	10 (2.2)	1.3	2 (0.9)	0.6	17 (1.2)	0.8	4 (0.5)	0.4
Blood lactate dehydrogenase increased	11 (2.5)	1.4	2 (0.9)	0.6	16 (1.1)	0.7	2 (0.3)	0.2
Muscular weakness	5 (1.1)	0.6	6 (2.7)	1.8	15 (1.1)	0.7	11 (1.4)	1.2
Thrombocytopenia	10 (2.2)	1.3	3 (1.4)	0.9	15 (1.1)	0.7	4 (0.5)	0.4
Hydronephrosis	3 (0.7)	0.4	3 (1.4)	0.9	13 (0.9)	0.6	16 (2.1)	1.7
Urinary tract obstruction	4 (0.9)	0.5	5 (2.3)	1.5	13 (0.9)	0.6	12 (1.5)	1.3
Hyperlipidaemia	11 (2.5)	1.4	1 (0.5)	0.3	12 (0.9)	0.6	2 (0.3)	0.2
Diabetes mellitus	6 (1.3)	0.8	9 (4.1)	2.8	11 (0.8)	0.5	14 (1.8)	1.5
Blood urea increased	7 (1.6)	0.9	5 (2.3)	1.5	10 (0.7)	0.5	9 (1.2)	1.0

COVID-19=Coronavirus disease 2019; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants, n=Number of participants with at least one row event; PY=Participant years; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Note: Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.

Most common study drug-related TEAEs

Table 31 Study drug-related TEAEs (reported in ≥1 % of participants) in either treatment arm - ARANOTE and ARANOTE+ARAMIS pool (SAF)

	ARANOTE				ARANOTE+ARAMIS			
	Darolutamide N=445		Placebo N=221		Darolutamide N=1399		Placebo N=775	
Preferred term	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Fatigue	10 (2.2)	1.3	8 (3.6)	2.4	78 (5.6)	3.7	32 (4.1)	3.5
Hot flush	10 (2.2)	1.3	5 (2.3)	1.5	46 (3.3)	2.2	20 (2.6)	2.2
Aspartate aminotransferase increased	25 (5.6)	3.2	10 (4.5)	3.0	35 (2.5)	1.6	10 (1.3)	1.1
Anaemia	24 (5.4)	3.1	5 (2.3)	1.5	33 (2.4)	1.5	7 (0.9)	0.7
Alanine aminotransferase increased	22 (4.9)	2.8	11 (5.0)	3.4	26 (1.9)	1.2	11 (1.4)	1.2
Hypertension	13 (2.9)	1.6	4 (1.8)	1.2	24 (1.7)	1.1	8 (1.0)	0.9
Nausea	0	0	1 (0.5)	0.3	24 (1.7)	1.1	18 (2.3)	1.9
Weight increased	19 (4.3)	2.4	6 (2.7)	1.8	20 (1.4)	0.9	7 (0.9)	0.7
Diarrhoea	2 (0.4)	0.2	0	0	17 (1.2)	0.8	9 (1.2)	1.0
Blood bilirubin increased	10 (2.2)	1.3	1 (0.5)	0.3	16 (1.1)	0.7	1 (0.1)	0.1
Gynaecomastia	0	0	1 (0.5)	0.3	15 (1.1)	0.7	4 (0.5)	0.4
Asthenia	5 (1.1)	0.6	3 (1.4)	0.9	14 (1.0)	0.6	10 (1.3)	1.1
Decreased appetite	0	0	3 (1.4)	0.9	14 (1.0)	0.6	9 (1.2)	1.0
Headache	1 (0.2)	0.1	1 (0.5)	0.3	14 (1.0)	0.6	5 (0.6)	0.5
Arthralgia	5 (1.1)	0.6	2 (0.9)	0.6	10 (0.7)	0.5	8 (1.0)	0.9
Rash	5 (1.1)	0.6	3 (1.4)	0.9	10 (0.7)	0.5	3 (0.4)	0.3
Blood creatinine increased	2 (0.4)	0.2	3 (1.4)	0.9	9 (0.6)	0.4	5 (0.6)	0.5
Neutropenia	2 (0.4)	0.2	3 (1.4)	0.9	8 (0.6)	0.4	4 (0.5)	0.4
Platelet count decreased	6 (1.3)	0.8	1 (0.5)	0.3	8 (0.6)	0.4	1 (0.1)	0.1
Hepatic function abnormal	5 (1.1)	0.6	0	0	7 (0.5)	0.3	1 (0.1)	0.1
Oedema peripheral	2 (0.4)	0.2	3 (1.4)	0.9	7 (0.5)	0.3	6 (0.8)	0.6
Bilirubin conjugated increased	6 (1.3)	0.8	1 (0.5)	0.3	6 (0.4)	0.3	1 (0.1)	0.1
Gamma-glutamyltransferase increased	5 (1.1)	0.6	0	0	6 (0.4)	0.3	0	0
Hyperglycaemia	5 (1.1)	0.6	1 (0.5)	0.3	6 (0.4)	0.3	2 (0.3)	0.2
Hyperkalaemia	2 (0.4)	0.2	3 (1.4)	0.9	6 (0.4)	0.3	3 (0.4)	0.3
Hyponatraemia	3 (0.7)	0.4	3 (1.4)	0.9	5 (0.4)	0.2	3 (0.4)	0.3

EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants, n=Number of participants with at least one row event; PY=Participant years; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.
EAIR = number of participants with the event / sum of exposure times, where exposure time is time to first occurrence if an event occurred, otherwise it is treatment duration and time at risk after treatment end, where time at risk after treatment end = time after end of treatment up to minimum of death date, data cut-off, open-label start, end of treatment-emergent window, lost to follow-up. For ARANOTE, withdrawal from study is also considered.
MedDRA Version 27.0.

Worst Grade 3 and 4 treatment-emergent adverse events

Table 32 TEAEs of worst Grade 3 or 4 in >0.5 % of participants in either treatment arm - ARANOTE and ARANOTE+ARAMIS pool (SAF)

	ARANOTE		ARANOTE+ARAMIS	
	Darolutamide N=445	Placebo N=221	Darolutamide N=1399	Placebo (N=775)
Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)
Hypertension	19 (4.3)	8 (3.6)	49 (3.5)	20 (2.6)
Anaemia	14 (3.1)	8 (3.6)	22 (1.6)	10 (1.3)
Urinary retention	2 (0.4)	1 (0.5)	17 (1.2)	12 (1.5)
Pneumonia	5 (1.1)	2 (0.9)	15 (1.1)	6 (0.8)
Aspartate aminotransferase increased	10 (2.2)	1 (0.5)	14 (1.0)	1 (0.1)
Urinary tract infection	8 (1.8)	1 (0.5)	14 (1.0)	4 (0.5)
Alanine aminotransferase increased	9 (2.0)	1 (0.5)	12 (0.9)	1 (0.1)
Haematuria	1 (0.2)	1 (0.5)	11 (0.8)	8 (1.0)
Bone pain	9 (2.0)	3 (1.4)	10 (0.7)	3 (0.4)
Hydronephrosis	3 (0.7)	2 (0.9)	10 (0.7)	5 (0.6)
Back pain	5 (1.1)	2 (0.9)	9 (0.6)	3 (0.4)
Acute kidney injury	3 (0.7)	1 (0.5)	8 (0.6)	3 (0.4)
Arthralgia	5 (1.1)	0	8 (0.6)	3 (0.4)
Fall	0	1 (0.5)	8 (0.6)	5 (0.6)
Urinary tract obstruction	3 (0.7)	1 (0.5)	8 (0.6)	2 (0.3)
Atrial fibrillation	1 (0.2)	0	7 (0.5)	2 (0.3)
Hyperkalaemia	3 (0.7)	1 (0.5)	7 (0.5)	4 (0.5)
Neutrophil count decreased	0	0	7 (0.5)	0
Spinal cord compression	5 (1.1)	1 (0.5)	5 (0.4)	1 (0.1)
Fatigue	0	1 (0.5)	4 (0.3)	6 (0.8)
Rash	3 (0.7)	0	4 (0.3)	0
Weight increased	4 (0.9)	1 (0.5)	4 (0.3)	1 (0.1)
Lymphopenia	1 (0.2)	2 (0.9)	3 (0.2)	5 (0.6)
Pain	3 (0.7)	2 (0.9)	3 (0.2)	2 (0.3)
Pathological fracture	3 (0.7)	2 (0.9)	3 (0.2)	2 (0.3)
Renal failure	2 (0.4)	0	3 (0.2)	4 (0.5)
Dyspnoea	0	1 (0.5)	2 (0.1)	4 (0.5)
Inguinal hernia	1 (0.2)	2 (0.9)	2 (0.1)	2 (0.3)
COVID-19	1 (0.2)	2 (0.9)	1 (<0.1)	2 (0.3)
Dysuria	0	0	1 (<0.1)	5 (0.6)
Pain in extremity	1 (0.2)	4 (1.8)	1 (<0.1)	5 (0.6)
Blood alkaline phosphatase increased	0	3 (1.4)	0	4 (0.5)
COVID-19 pneumonia	0	2 (0.9)	0	2 (0.3)
Cancer pain	0	2 (0.9)	0	2 (0.3)
Gastroenteritis radiation	0	2 (0.9)	0	2 (0.3)
Headache	0	2 (0.9)	0	3 (0.4)
Hypercalcaemia	0	2 (0.9)	0	2 (0.3)
Weight decreased	0	2 (0.9)	0	2 (0.3)

COVID-19=Coronavirus disease 2019; EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants; n=Number of participants with at least one row event; PY=Participant years; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Study drug-related Grade 3 and 4 TEAEs

Table 33 Incident of study drug-related Grade 3 or 4 TEAEs in ≥0.5 % of participants in either treatment arm - ARANOTE and ARANOTE+ARAMIS pool (SAF)

	ARANOTE		ARANOTE+ARAMIS	
	Darolutamide (N=445)	Placebo (N=221)	Darolutamide (N=1399)	Placebo (N=775)
Preferred term	n (%)	n (%)	n (%)	n (%)
Hypertension	8 (1.8)	1 (0.5)	12 (0.9)	4 (0.5)
Alanine aminotransferase increased	6 (1.3)	0	8 (0.6)	0
Aspartate aminotransferase increased	5 (1.1)	0	8 (0.6)	0
Anaemia	3 (0.7)	0	4 (0.3)	0
Rash	3 (0.7)	0	3 (0.2)	0

EAIR=exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants, n=Number of participants with at least one row event; PY=participant years; SAF=safety analysis set; TEAE=treatment-emergent adverse event

Note: Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.

Relationship to study drug is based on investigator assessment.

Table 34 Incidence of special topics TEAEs - ARANOTE and ARANOTE+ARAMIS pool (SAF)

	ARANOTE				ARANOTE+ARAMIS			
	Darolutamide (N=445)		Placebo (N=221)		Darolutamide (N=1399)		Placebo (N=775)	
Special topics TEAE grouped term	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Fatigue/ asthenic conditions	41 (9.2)	5.4	28 (12.7)	9.0	192 (13.7)	9.6	91 (11.7)	10.4
Bone fractures excluding pathological fractures	18 (4.0)	2.3	5 (2.3)	1.5	58 (4.1)	2.7	25 (3.2)	2.7
Fall	6 (1.3)	0.8	2 (0.9)	0.6	46 (3.3)	2.1	28 (3.6)	3.0
Diabetes mellitus and hyperglycemia	40 (9.0)	5.3	21 (9.5)	6.7	62 (4.4)	2.9	33 (4.3)	3.6
Breast disorders/gynecomastia	6 (1.3)	0.8	2 (0.9)	0.6	28 (2.0)	1.3	11 (1.4)	1.2
Vasodilatation and flushing	41 (9.2)	5.6	16 (7.2)	5.0	95 (6.8)	4.6	39 (5.0)	4.3
Rash	19 (4.3)	2.4	8 (3.6)	2.4	47 (3.4)	2.2	13 (1.7)	1.4
Hypertension	42 (9.4)	5.5	21 (9.5)	6.7	112 (8.0)	5.4	54 (7.0)	6.0
Cardiac disorders	55 (12.4)	7.3	20 (9.0)	6.3	158 (11.3)	7.7	58 (7.5)	6.4
Cardiac arrhythmias	39 (8.8)	5.1	15 (6.8)	4.7	103 (7.4)	4.9	37 (4.8)	4.0
Coronary artery disorders	16 (3.6)	2.0	3 (1.4)	0.9	47 (3.4)	2.2	17 (2.2)	1.8
Heart failures	4 (0.9)	0.5	2 (0.9)	0.6	22 (1.6)	1.0	7 (0.9)	0.7
Cerebral ischaemia	1 (0.2)	0.1	3 (1.4)	0.9	14 (1.0)	0.6	11 (1.4)	1.2
Cerebral and intracranial hemorrhage	2 (0.4)	0.2	1 (0.5)	0.3	4 (0.3)	0.2	3 (0.4)	0.3
Seizure	0	0	0	0	2 (0.1)	0.1	1 (0.1)	0.1
Mental impairment disorders	7 (1.6)	0.9	1 (0.5)	0.3	23 (1.6)	1.1	11 (1.4)	1.2
Depressed mood disorders	2 (0.4)	0.2	2 (0.9)	0.6	19 (1.4)	0.9	10 (1.3)	1.1
Weight decreased	14 (3.1)	1.8	6 (2.7)	1.8	48 (3.4)	2.2	18 (2.3)	1.9
Interstitial lung disease	1 (0.2)	0.1	1 (0.5)	0.3	7 (0.5)	0.3	1 (0.1)	0.1
Additional primary malignancies	12 (2.7)	1.5	2 (0.9)	0.6	39 (2.8)	1.8	17 (2.2)	1.8

EAIR=Exposure-adjusted incidence rate, MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants, n=Number of participants with at least one row event; PY=Participant years; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Note: Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.
EAIR = number of participants with the event / sum of exposure times, where exposure time is time to first occurrence if an event occurred, otherwise it is treatment duration and time at risk after treatment end, where time at risk after treatment end = time after end of treatment up to minimum of death date, data cut-off, open-label start, end of treatment-emergent window, lost to follow-up. For ARANOTE, withdrawal from study is also considered.
MedDRA Version 27.0.

Adverse drug reactions (ADRs)

Since ARANOTE and ARAMIS included patients with prostate cancer treated with darolutamide at the same posology, their safety data were pooled to support the update of section 4.8 of the SmPC reflecting adverse drug reaction.

Table 35 Adverse reactions frequencies reported in mHSPC patients treated with darolutamide in ARAMIS and ARANOTE studies[a]

System organ class (MedDRA)	Very common	Common
Cardiac disorders		Ischaemic heart disease[b] **(3.4%)** Heart failure[c] **(1.6%)**
Skin and subcutaneous tissue disorders		Rash **(3.4%)**
Musculoskeletal and connective tissue disorders		Pain in extremity **(6.6%)** Fractures **(4.1%)**
General disorders and administration site conditions	Fatigue/asthenic conditions[e] **(13.7%)**	
Investigations[f]	Neutrophil count decreased **(17.3%)** Blood bilirubin increased **(16.1%)** ALT increased **(13.3%)** AST increased **(22.0%)**	

[a] The median duration of exposure in the ARAMIS and ARANOTE studies was 18.2 months (range: 0.0 to 44.3 months) in patients treated with darolutamide and 11.6 months (range: 0.0 to 40.5 months) in patients treated with placebo.

[b] Includes arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischaemia.

[c] Includes cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock, heart failure with preserved ejection fraction.

[d] Includes rash, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, dermatitis.

[e] Includes fatigue and asthenia, lethargy and malaise.

[f] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The incidence is based on values reported as laboratory abnormalities.

Serious adverse event/deaths/other significant events

Deaths

Table 36 Overview of all death- ARANOTE (SAF)

Deaths Cause of death	Darolutamide N=445 n (%)	Placebo N=221 n (%)
All deaths	**105 (23.6)**	**61 (27.6)**
AE associated with clinical disease progression	3 (0.7)	2 (0.9)
AE not associated with clinical disease progression	12 (2.7)	9 (4.1)
Other	12 (2.7)	2 (0.9)
Progressive disease	60 (13.5)	41 (18.6)
Unknown	18 (4.0)	7 (3.2)
Death within 30 days after the first dose of the study drug	**0**	**0**
Death during the period from the first to last dose of the study drug	**2 (0.4)**	**0**
AE associated with clinical disease progression	0	0
AE not associated with clinical disease progression	0	0
Other	1 (0.2)	0
Progressive disease	0	0
Unknown	1 (0.2)	0
Death within 30 days after the last dose of the study drug	**25 (5.6)**	**15 (6.8)**
AE associated with clinical disease progression	1 (0.2)	2 (0.9)
AE not associated with clinical disease progression	9 (2.0)	7 (3.2)
Other	3 (0.7)	0
Progressive disease	9 (2.0)	4 (1.8)
Unknown	3 (0.7)	2 (0.9)
Death later than 30 days after the last dose of the study drug	**76 (17.1)**	**45 (20.4)**
AE associated with clinical disease progression	2 (0.4)	0
AE not associated with clinical disease progression	3 (0.7)	2 (0.9)
Other	8 (1.8)	2 (0.9)
Progressive disease	51 (11.5)	37 (16.7)
Unknown	12 (2.7)	4 (1.8)

AE=Adverse event; N=Total number of participants (100%); n=Number of participants with event; SAF=Safety analysis set

TEAEs with a fatal outcome (Grade 5)

Table 37 Incident of all Grade 5 TEAEs by MedDRA-PT - ARANOTE (SAF)

MedDRA PT	Darolutamide N=445 n (%)	Placebo N=221 n (%)
Death	2 (0.4)	2 (0.9)
Craniocerebral injury	2 (0.4)	0
Myocardial infarction	2 (0.4)	0
Septic shock	2 (0.4)	0
Sepsis	1 (0.2)	1 (0.5)
Acinetobacter sepsis	1 (0.2)	0
COVID-19 pneumonia	1 (0.2)	0
Disease progression	1 (0.2)	0
Dyspnoea	1 (0.2)	0
Hyponatraemia	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.2)	0
Oncologic complication	1 (0.2)	0
Pneumonia viral	1 (0.2)	0
Prostate cancer metastatic	1 (0.2)	0
Pulmonary oedema	1 (0.2)	0
Pulmonary sepsis	1 (0.2)	0
SARS-CoV-2 test positive	1 (0.2)	0
Sudden death	1 (0.2)	0
Urinary tract infection	1 (0.2)	0
Urosepsis	1 (0.2)	0
Acute coronary syndrome	0	1 (0.5)
Acute myocardial infarction	0	1 (0.5)
Cardiac arrest	0	1 (0.5)
Cerebral infarction	0	1 (0.5)
Gastrointestinal haemorrhage	0	1 (0.5)
Intestinal ischaemia	0	1 (0.5)
Ischaemic stroke	0	1 (0.5)
Pulmonary congestion	0	1 (0.5)
Pulmonary embolism	0	1 (0.5)
Renal failure	0	1 (0.5)
Respiratory failure	0	1 (0.5)

COVID-19=Coronavirus disease 2019; CTCAE Version 5.0=Common Terminology Criteria for Adverse Events Version 5.0; MedDRA Version 27.0=Medical Dictionary for Regulatory Activities Version 27.0; N=Total number of participants (100%); n=Number of participants with event; PT=Preferred term; SAF=Safety analysis set; SARS-CoV-2=Severe acute respiratory syndrome coronavirus 2; TEAE=Treatment-emergent adverse event
Note: Participants may have >1 entry.
CTCAE Version 5.0 and MedDRA Version 27.0.

Serious adverse events

Table 38 Incident of TEAEs reported in >1% of participants in either treatment arm - ARANOTE and ARANOTE+ARAMIS pool (SAF)

	ARANOTE				ARANOTE+ARAMIS			
	Darolutamide N=445		Placebo N=221		Darolutamide N=1399		Placebo N=775	
Preferred term	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Pneumonia	6 (1.3)	0.7	2 (0.9)	0.6	21 (1.5)	1.0	8 (1.0)	0.9
Urinary retention	3 (0.7)	0.4	1 (0.5)	0.3	18 (1.3)	0.8	19 (2.5)	2.0
Urinary tract infection	8 (1.8)	1.0	1 (0.5)	0.3	15 (1.1)	0.7	1 (0.1)	0.1
Anaemia	3 (0.7)	0.4	3 (1.4)	0.9	5 (0.4)	0.2	3 (0.4)	0.3
Spinal cord compression	5 (1.1)	0.6	0	0	5 (0.4)	0.2	0	0

EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants, n=Number of participants with at least one row event; PY=Participant years; SAF=Safety analysis set; TESAE=Treatment-emergent serious adverse event

Note: Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.
EAIR = number of participants with the event / sum of exposure times, where exposure time is time to first occurrence if an event occurred, otherwise it is treatment duration and time at risk after treatment end, where time at risk after treatment end = time after end of treatment up to minimum of death date, data cut-off, open-label start, end of treatment-emergent window, lost to follow-up. For ARANOTE, withdrawal from study is also considered.
MedDRA Version 27.0.

Study drug-related TESAEs

No study drug-related TESAEs occurred in the darolutamide arm in >1 participant. For most participants with study drug-related TESAEs, the worst grade of these TESAEs was Grade 3. Study drug-related TESAEs with a worst Grade of 3 in severity were reported in 1.6% of participants in the darolutamide arm (systemic inflammatory response syndrome, hepatic function abnormal, urinary tract infection, pelvic fracture, ALT increased, AST increased, bladder neck obstruction, and renal failure) and in 2.3% of participants in the placebo arm (AV block, GI hemorrhage, gait disturbance, PS decreased, decreased appetite, pain in extremity, dizziness, and Guillain-Barre syndrome).

Study drug-related TESAEs with Grade 4 as the worst grade were observed in 0% of participants in the darolutamide arm (no event) and in 0.9% of participants in the placebo arm (cardiac failure congestive, acute kidney injury, and hydronephrosis).

Laboratory findings

Table 39 Incident of haematology and general chemistry abnormalities worsening from baseline during treatment period. ARANOTE (SAF)

	Darolutamide N=445 (100%)		Placebo N=221 (100%)	
CTCAE term	All Grades n (%)	Grades 3 or 4 n (%)	All Grades n (%)	Grades 3 or 4 n (%)
Hematology				
Anemia	219 (50.5)	14 (3.2)	92 (43.0)	8 (3.7)
Lymphocyte count decreased	99 (22.8)	8 (1.8)	38 (17.8)	9 (4.2)
White blood cell decreased	75 (17.3)	3 (0.7)	17 (7.9)	1 (0.5)
Neutrophil count decreased	68 (15.7)	5 (1.2)	20 (9.3)	1 (0.5)
Platelet count decreased	67 (15.4)	4 (0.9)	20 (9.3)	0
Lymphocyte count increased	4 (0.9)	0	4 (1.9)	0
Hemoglobin increased	3 (0.7)	0	1 (0.5)	0
Leukocytosis	0	0	0	0
Chemistry				
Hyperglycemia	186 (43.4)	17 (4.0)	106 (50.7)	13 (6.2)
Aspartate aminotransferase increased	136 (31.5)	12 (2.8)	53 (24.8)	1 (0.5)
Alanine aminotransferase increased	121 (27.9)	9 (2.1)	50 (23.4)	1 (0.5)
Creatinine increased	83 (19.2)	3 (0.7)	42 (19.7)	2 (0.9)
Alkaline phosphatase increased	74 (17.2)	3 (0.7)	42 (20.2)	5 (2.4)
Blood bilirubin increased	72 (16.7)	2 (0.5)	14 (6.6)	0
Hyperkalemia	72 (16.6)	9 (2.1)	36 (16.8)	2 (0.9)
Hypercalcemia	69 (16.1)	0	35 (16.7)	2 (1.0)
Hypocalcemia	53 (12.4)	4 (0.9)	18 (8.6)	0
Hypoalbuminemia	44 (10.2)	0	25 (11.8)	0
Hypernatremia	27 (6.3)	0	13 (6.1)	2 (0.9)
Hypoglycemia	13 (3.0)	0	4 (1.9)	0

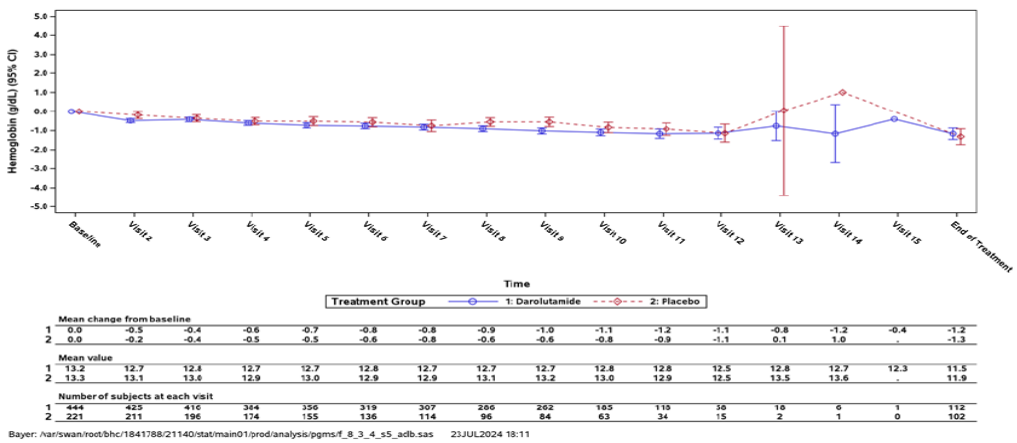
CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of participants (100%); n=Number of participants with event; SAF=Safety Analysis Set

Anemia

Anemia was reported as post baseline laboratory abnormality for 50.5% of participants in the darolutamide arm and for 43.0% in the placebo arm in ARANOTE. For most participants with this abnormality, the worst post baseline CTCAE grade was Grade 1 or 2:

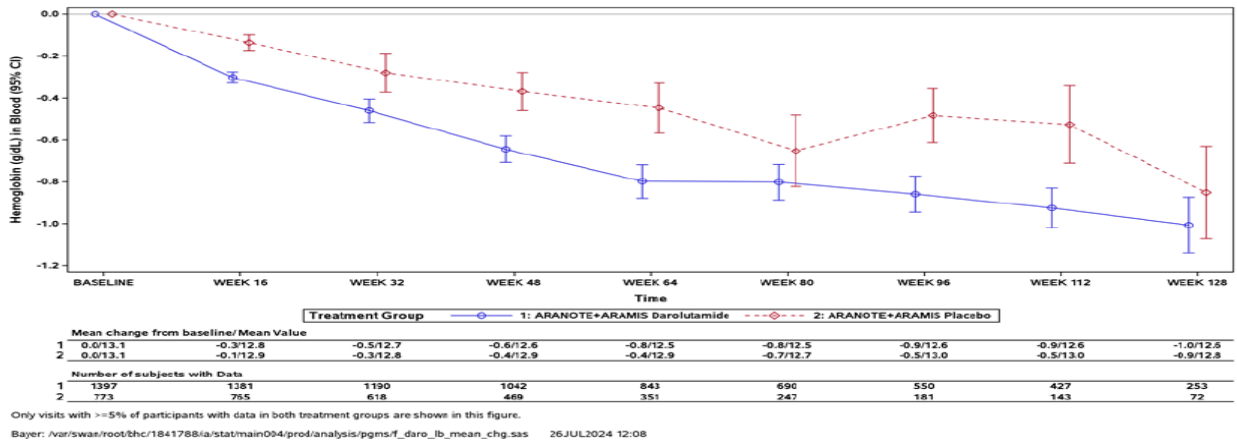
- Any Grade (darolutamide vs placebo): 50.5% vs 43.0%
- Grade 1: 37.6% vs 29.4%
- Grade 2: 9.7% vs 9.8%
- Grade 3: 3.2% vs 3.7%

Figure 14 Haemoglobin (g/dL): mean change from baseline over time in ARANOTE (SAF)



The results for the ARANOTE+ARAMIS pool were consistent with results from ARANOTE (data not shown) The incidence of anemia as a post baseline laboratory abnormality was higher for the darolutamide arm (44.4%) vs the placebo arm (33.9%), with the worst post baseline abnormality most commonly Grade 1 or 2 for most participants with anemia.

Figure 15 Haemoglobin (g/dL): mean change from baseline over time in ARANOTE and ARANOTE+ARAMIS pool (SAF)



Platelet Count Decreased

Platelet count decreased was reported as a post baseline laboratory abnormality for 15.4% of participants in the darolutamide arm and for 9.3% in the placebo arm in ARANOTE. For most participants with this abnormality, the worst post baseline CTCAE grade was Grade 1:

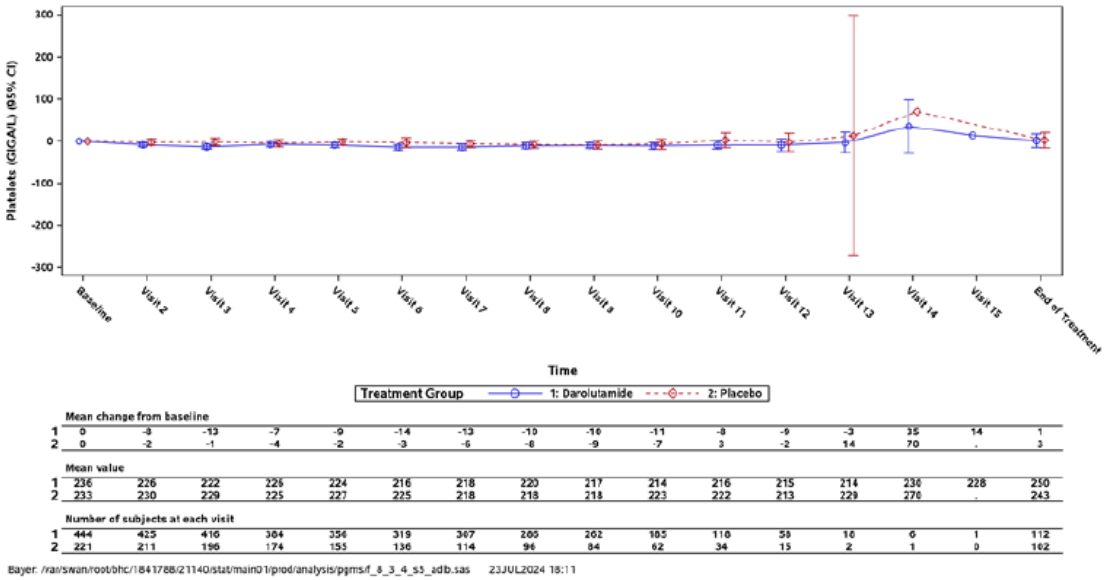
- Any Grade (darolutamide vs placebo): 15.4% vs 9.3%
- Grade 1: 13.1% vs 8.9%
- Grade 2: 1.4% vs 0.5%
- Grade 3: 0.5% vs 0%
- Grade 4: 0.5% vs 0%

Thrombocytopenia as a TEAE was reported for 2.2% of participants in the darolutamide arm and for 1.4% of participants in the placebo arm in ARANOTE. For most participants with TEAEs of thrombocytopenia, the worst CTCAE grade was Grade 1 or 2:

- Any Grade (darolutamide vs placebo): 2.2% vs 1.4% (EAIRs per 100 PY: 1.3 vs 0.9)
- Grade 1: 1.3% vs 1.4%
- Grade 2: 0.7% vs 0%
- Grade 3: 0.2% vs 0%

Mean change from baseline over time in the level of platelets appeared similar between the treatment arms in ARANOTE.

Figure 16 Platelets (GIGA/L) mean change from baseline over time in ARANOTE (SAF)



White Blood Cell Count Decreased

WBC count decreased was reported as a post baseline laboratory abnormality for 17.3% of participants in the darolutamide arm and for 7.9% in the placebo arm in ARANOTE. For most participants with this abnormality, the worst post baseline CTCAE grade was Grade 1 or 2:

• Any Grade (darolutamide vs placebo): 17.3% vs 7.9%

• Grade 1: 12.9% vs 5.6%

• Grade 2: 3.7% vs 1.9%

• Grade 3: 0.5% vs 0.5%

• Grade 4: 0.2% vs 0%

Leukopenia as a TEAE was reported for 1.6% of participants in the darolutamide arm and for 1.4% of participants in the placebo arm in ARANOTE. For all participants with TEAEs of leukopenia, the worst CTCAE grade was Grade 1 or 2:

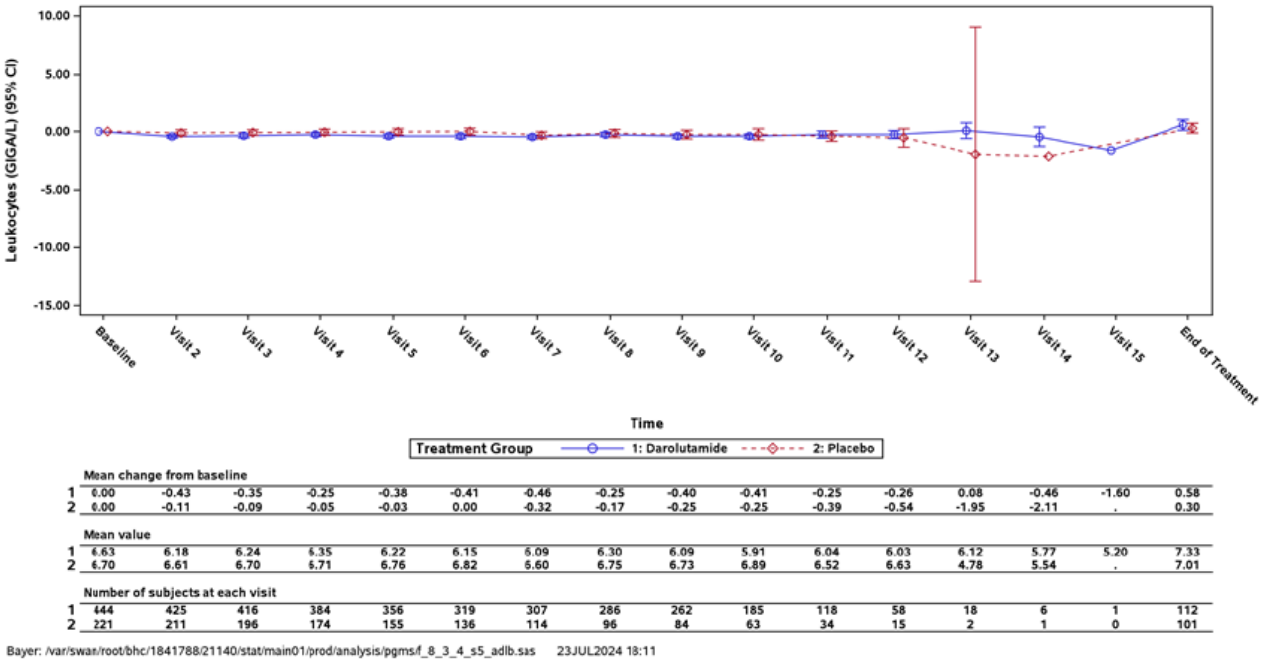
• Any Grade (darolutamide vs placebo): 1.6% vs 1.4% (EAIRs per 100 PY: 0.9 vs 0.9)

• Grade 1: 1.1% vs 1.4%

• Grade 2: 0.4% vs 0%

Mean change from baseline over time in WBC counts appeared to be similar between the treatment arms in ARANOTE.

Figure 17 Leukocytes (GIGA/L): mean change from baseline over time in ARANOTE (SAF)



Mean change from baseline

1	0.00	-0.43	-0.35	-0.25	-0.38	-0.41	-0.46	-0.25	-0.40	-0.41	-0.25	-0.26	0.08	-0.46	-1.60	0.58
2	0.00	-0.11	-0.09	-0.05	-0.03	0.00	-0.32	-0.17	-0.25	-0.25	-0.39	-0.54	-1.95	-2.11	.	0.30

Mean value

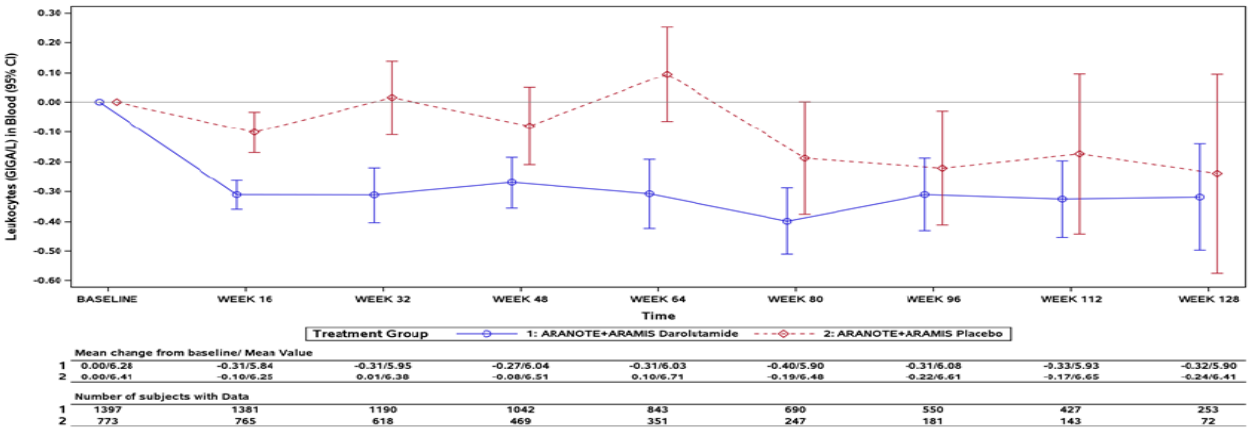
1	6.63	6.18	6.24	6.35	6.22	6.15	6.09	6.30	6.09	5.91	6.04	6.03	6.12	5.77	5.20	7.33
2	6.70	6.61	6.70	6.71	6.76	6.82	6.60	6.75	6.73	6.89	6.52	6.63	4.78	5.54	.	7.01

Number of subjects at each visit

1	444	425	416	384	356	319	307	286	262	185	118	58	18	6	1	112
2	221	211	196	174	155	136	114	96	84	63	34	15	2	1	0	101

Bayer: /var/swan/root/bhc/1841788/21140/stat/main01/prod/analysis/pgms/f_8_3_4_s5_adlb.sas 23JUL2024 18:11

Figure 18 Leukocytes (GIGA/L): mean change from baseline over time in ARANOTE and ARANOTE+ARAMIS pool (SAF)



Mean change from baseline/ Meas Value

1	0.00/6.28	-0.31/5.84	-0.31/5.95	-0.27/6.04	-0.31/6.03	-0.40/5.90	-0.31/6.08	-0.33/5.93	-0.32/5.90
2	0.00/6.41	-0.10/6.25	0.01/6.38	-0.08/6.51	0.10/6.71	-0.19/6.48	-0.22/6.61	-0.17/6.65	-0.24/6.41

Number of subjects with Data

1	1397	1381	1190	1042	843	690	550	427	253
2	773	765	618	469	351	247	181	143	72

Only visits with >=5% of participants with data in both treatment groups are shown in this figure.

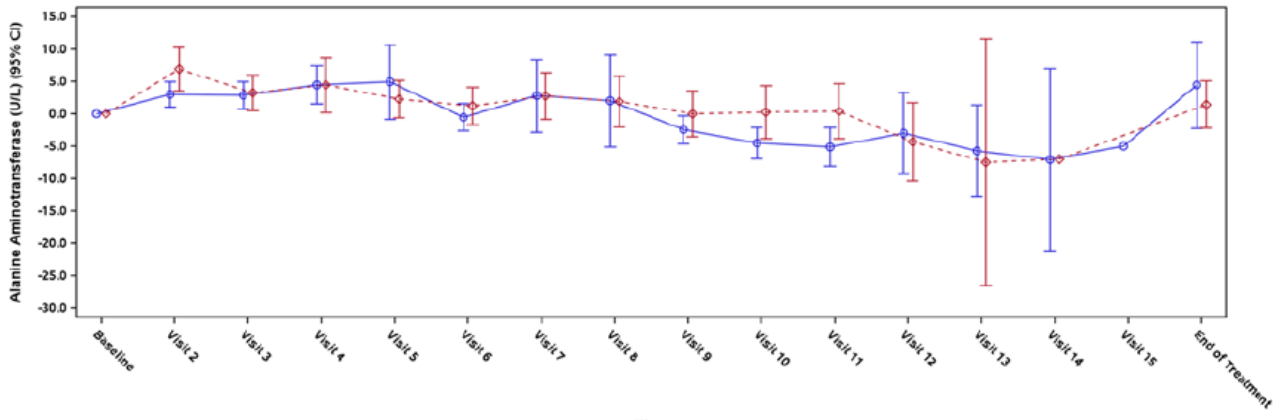
Bayer: /var/swan/root/bhc/1841788/a/stat/main004/prod/analysis/pgms/f_daro_lb_mean_chg.sas 26JUL2024 12:08

Alanine aminotransferase

In ARANOTE, baseline ALT values were measured in 445 participants in the darolutamide arm and in 221 participants in the placebo arm. Mean ALT values at baseline were 24.7 U/L in the darolutamide arm vs 23.5 U/L in the placebo arm.

Mean change from baseline over time in the level of ALT appeared to be similar between the treatment arms in ARANOTE.

Figure 19 ALT (U/L) mean change from baseline over time in ARANOTE (SAF)



Mean change from baseline

1	0.0	3.0	2.8	4.5	4.9	-0.5	2.8	2.0	-2.5	-4.5	-5.1	-3.0	-5.7	-7.1	-5.0	4.4
2	0.0	6.9	3.2	4.5	2.3	1.2	2.7	1.9	0.0	0.2	0.4	-4.3	-7.5	-7.0	.	1.4

Mean value

1	24.7	27.7	27.7	29.4	30.2	25.1	28.5	27.8	23.4	22.2	21.9	23.2	19.1	20.1	11.0	28.7
2	23.5	30.7	26.7	28.4	26.0	25.0	26.6	25.6	23.9	24.8	23.4	20.2	18.5	22.0	.	25.3

Number of subjects at each visit

1	445	425	415	384	354	317	307	285	262	185	118	57	18	6	1	112
2	221	210	195	174	155	136	114	97	83	63	34	15	2	1	0	101

The TEAE of ALT increased in ARANOTE was reported with a comparable incidence between the darolutamide and the placebo arms (9.0%, EAIR 5.3 vs 8.1%, EAIR 5.6, respectively). Drug-related TEAE incidence for ALT increased was similar in the darolutamide arm compared to the placebo arm (4.9% vs 5.0%). The incidence of Grade 3 or 4 ALT increased was slightly higher in the darolutamide arm compared to placebo arm (2.0% vs 0.5% respectively) The incidence of Grade 3 or 4 drug-related ALT increased was slightly higher in darolutamide arm compared to placebo arm (1.3% vs 0%).

ALT increased

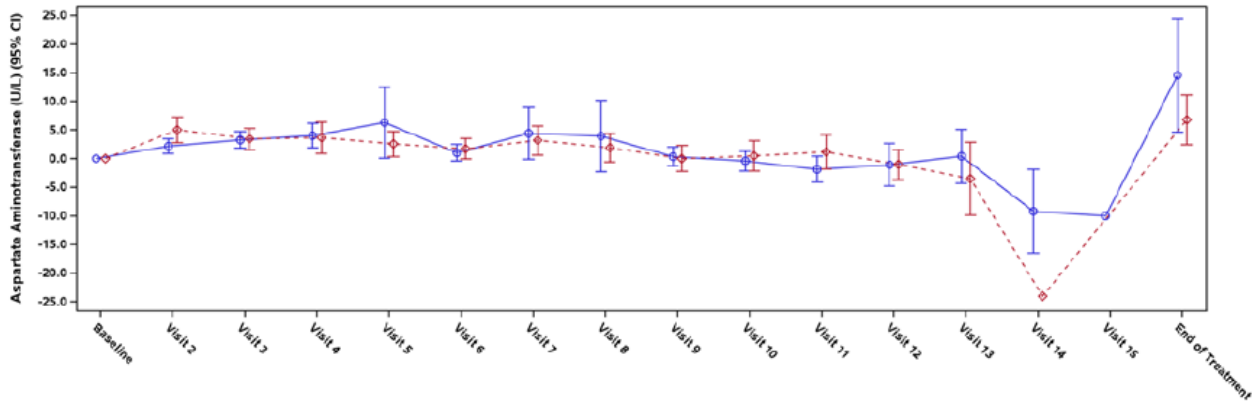
ALT was reported as a laboratory abnormality in 13.3% of patients treated with darolutamide and in 9.7% of patients treated with placebo. ALT increased of grade 3 and 4 was reported in 0.9% of patients treated with darolutamide and in 0.3% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased ALT was 253 days and for increased AST 257 days. The mean duration of the first episode was 122 days for ALT increase and 121 days for AST increase. (data not shown)

Aspartate aminotransferase

In ARANOTE, baseline AST values were measured in 445 participants in the darolutamide arm and in 221 participants in the placebo arm. Mean AST values at baseline were similar between the treatment arms, with 26.4 U/L in the darolutamide arm vs 24.8 U/L in the placebo arm.

Mean change from baseline over time in the level of AST appeared to be similar between the treatment arms in ARANOTE.

Figure 20 AST (U/L): mean change from baseline over time in ARANOTE (SAF)



	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	End of Treatment
Mean change from baseline																
1	0.0	2.2	3.3	4.0	6.3	1.1	4.4	3.9	0.4	-0.4	-1.9	-1.1	0.4	-9.2	-10.0	14.6
2	0.0	5.0	3.4	3.6	2.6	1.7	3.2	1.9	0.0	0.5	1.1	-1.0	-3.5	-24.0	.	6.8
Mean value																
1	26.4	28.4	29.4	29.9	32.4	27.3	30.7	30.3	26.8	26.4	24.9	26.2	26.1	17.5	13.0	41.3
2	24.8	29.7	27.9	28.3	27.1	26.2	27.4	26.0	24.3	24.7	24.8	21.9	27.0	9.0	.	31.4
Number of subjects at each visit																
1	445	422	411	381	350	312	305	285	251	183	117	58	17	6	1	112
2	221	209	196	174	155	135	114	97	83	63	34	15	2	1	0	101

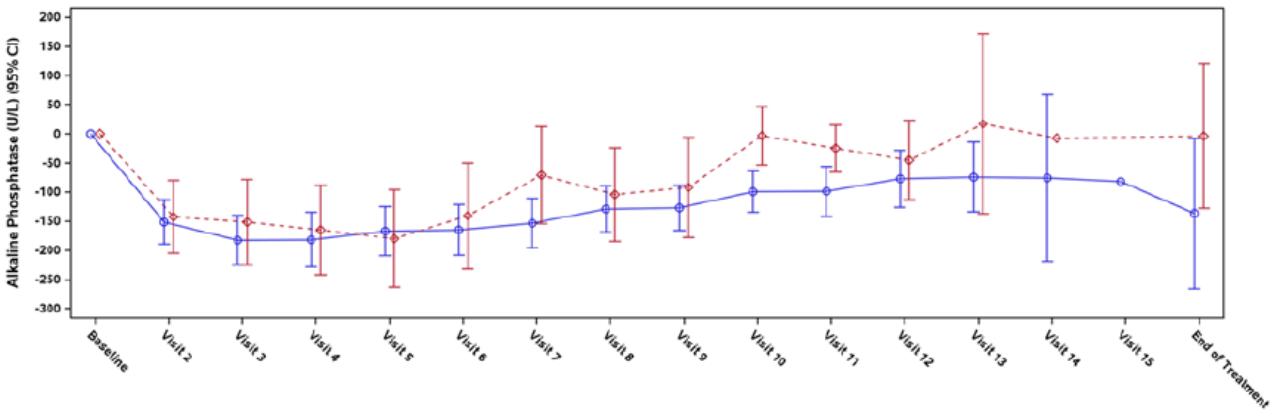
AST=Aspartate aminotransferase; SAF=Safety analysis set

In ARANOTE, the TEAE of AST increased was reported with a higher incidence in the darolutamide arm than in the placebo arm (9.7%, EAIR 5.7 vs 7.7%, EAIR 5.3, respectively). Drug-related TEAE incidence for AST increased was slightly higher in the darolutamide arm compared to the placebo arm (5.6% vs 4.5%)). The incidence of Grade 3 or 4 AST increased was slightly higher in the darolutamide arm compared to the placebo arm (2.2% vs 0.5%, respectively). The incidence of Grade 3 or 4 drug-related AST increased was slightly higher in the darolutamide arm compared to the placebo arm (1.1% vs 0%).

Alkaline phosphatase

In ARANOTE, baseline ALP values were measured in 442 participants in the darolutamide arm and in 215 participants in the placebo arm. Mean ALP values at baseline were lower in the darolutamide arm compared to the placebo arm (314 U/L vs 331 U/L). Mean change from baseline over time in the levels of ALP appeared to be similar between the treatment arms in ARANOTE.

Figure 21 ALP (U/L): mean change from baseline over time in ARANOTE (SAF)



Mean change from baseline																
1	0	-151	-183	-182	-167	-165	-153	-129	-127	-99	-99	-77	-74	-76	-82	-137
2	0	-142	-152	-165	-180	-141	-71	-104	-92	-3	-25	-45	17	-7	.	-4
Mean value																
1	314	160	127	127	112	106	110	109	103	104	101	98	99	84	64	310
2	331	191	173	145	137	146	149	112	111	146	126	94	65	53	.	357
Number of subjects at each visit																
1	442	424	412	382	354	317	307	285	262	184	116	57	18	6	1	111
2	215	207	196	173	154	136	114	97	82	63	34	15	2	1	0	101

ALP=Alkaline phosphatase; SAF=Safety analysis set

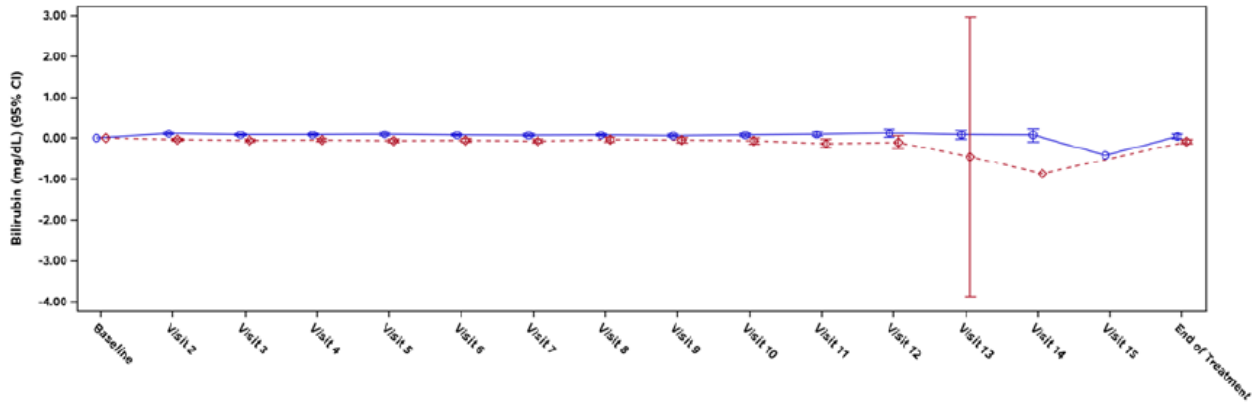
In ARANOTE, the TEAE of ALP increased was reported with a slightly higher incidence but similar EAIR in the darolutamide arm compared with the placebo arm (6.7% with EAIR of 3.8 vs 5.9% with EAIR of 3.9 respectively). Drug-related TEAE incidence for ALP increased was balanced between the darolutamide and the placebo arms (0.4% vs 0.9%). All reports of a TEAE of ALP increased were of Grade 1 or 2 (or 3 only in the placebo arm) and none led to permanent drug discontinuation or dose reductions.

Total bilirubin

In ARANOTE, baseline TBL values were measured in 445 participants in the darolutamide arm and in 221 participants in the placebo arm. Mean TBL values at baseline were similar between the darolutamide and the placebo arms (0.62 mg/dL vs 0.63 mg/dL).

Mean change from baseline over time in the levels of TBL appeared to be similar between the treatment arms in ARANOTE.

Figure 22 TBL (U/L): mean change from baseline over time in ARANOTE (SAF)



	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	End of Treatment
Mean change from baseline																
1	0.00	0.12	0.08	0.09	0.10	0.08	0.07	0.08	0.06	0.08	0.10	0.13	0.09	0.08	-0.41	0.04
2	0.00	-0.04	-0.05	-0.04	-0.06	-0.05	-0.07	-0.03	-0.05	-0.07	-0.13	-0.10	-0.45	-0.86	.	-0.08
Mean value																
1	0.62	0.74	0.71	0.71	0.73	0.72	0.71	0.72	0.71	0.73	0.74	0.77	0.76	0.72	0.47	0.61
2	0.63	0.60	0.58	0.61	0.59	0.61	0.60	0.64	0.63	0.64	0.60	0.57	0.59	0.46	.	0.54
Number of subjects at each visit																
1	445	423	415	383	352	317	307	285	252	185	118	58	18	6	1	112
2	221	210	195	174	155	136	113	97	83	63	34	15	2	1	0	102

SAF=Safety analysis set; TBL=Total bilirubin

In ARANOTE, the TEAE of blood bilirubin increased was reported with a higher incidence in the darolutamide arm than in the placebo arm (4.3%, EAIR of 2.4 vs 0.9%, EAIR of 0.6 respectively). Drug-related TEAE incidence for blood bilirubin increased was slightly higher in the darolutamide arm compared to the placebo arm (2.2% vs 0.5%) (Table 2-3). All but 1 participant (Grade 3 in the darolutamide arm) with TEAEs of blood bilirubin increased had events of Grade 1 or 2 and 1 participant (Grade 2 in the darolutamide arm) had a TEAE of blood bilirubin increased that led to permanent study drug discontinuation.

Two participants (both in the darolutamide arm) had TEAEs of blood bilirubin increased that led to study drug interruption.

Hy's law and drug-induced liver injury

Two cases in the darolutamide arm were identified in the listing, of which 1 participant fulfilled the biochemical criteria for Hy's law (ALT and/or AST ≥ 3 x ULN and total bilirubin >2 x ULN with ALP <2 x ULN). The second participant had ALT and AST both ≥3 x ULN and TBL >2 x ULN but the ALP was ≥2 x ULN; thus, not meeting the biochemical criteria for Hy's law. There was no participant fulfilling Hy's law criteria in the placebo arm.

Based on one of these cases meeting the biochemical criteria of Hy's law, the CCDS was updated in April 2023 to include a new warning on hepatotoxicity.

TEAEs of SMQ "Drug-related hepatic disorders"

TEAEs reported in the SMQ "Drug-related hepatic disorders" most commonly had a worst Grade of 1 or 2 in both the darolutamide (14.2% and 5.6% of participants, respectively) and the placebo arms (11.3% and 3.6%). TEAEs in this SMQ, with a worst Grade of 3 or 4, occurred in 2.2% and 0.7% of participants in the darolutamide arm and in 2.3% and 0% of participants in the placebo arm, respectively. There were no Grade 5 events in this SMQ. The TEAE DILI occurred with low incidence (darolutamide: 2 [0.4%] vs placebo: 0%). The 2 TEAEs of DILI reported in the darolutamide arm had a severity of Grade 1 and Grade 2.

Table 40 TEAEs reported in the SMQ "Drug-related hepatic disorders

	Darolutamide (N=445)		Placebo (N=221)	
	n (%)	EAIR per 100 PY	n (%)	EAIR per 100 PY
Number (%) of participants with at least 1 narrow scope PT	80 (18.0)	11.3	28 (12.7)	9.1
Number of participants with at least 1 narrow or broad scope PT	101 (22.7)	14.6	38 (17.2)	12.6
Narrow scope PTs				
Alanine aminotransferase increased	40 (9.0)	5.3	18 (8.1)	5.6
Ascites	0	0	1 (0.5)	0.3
Aspartate aminotransferase increased	43 (9.7)	5.7	17 (7.7)	5.3
Bilirubin conjugated increased	8 (1.8)	1.0	1 (0.5)	0.3
Blood bilirubin increased	19 (4.3)	2.4	2 (0.9)	0.6
Blood bilirubin unconjugated increased	3 (0.7)	0.4	1 (0.5)	0.3
Chronic hepatitis	2 (0.4)	0.2	0	0
Drug-induced liver injury	2 (0.4)	0.2	0	0
Gamma-glutamyltransferase increased	8 (1.8)	1.0	2 (0.9)	0.6
Hepatic cirrhosis	1 (0.2)	0.1	0	0
Hepatic cyst	1 (0.2)	0.1	0	0
Hepatic enzyme increased	1 (0.2)	0.1	0	0
Hepatic function abnormal	7 (1.6)	0.9	0	0
Hepatic steatosis	2 (0.4)	0.2	1 (0.5)	0.3
Hepatomegaly	2 (0.4)	0.2	0	0
Hyperbilirubinaemia	4 (0.9)	0.5	0	0
Jaundice	2 (0.4)	0.2	0	0
Liver injury	2 (0.4)	0.2	0	0
Transaminases increased	1 (0.2)	0.1	0	0
Broad scope PTs				
Blood alkaline phosphatase increased	30 (6.7)	3.8	13 (5.9)	3.9
Hypoalbuminaemia	6 (1.3)	0.8	1 (0.5)	0.3
Urobilinogen urine increased	1 (0.2)	0.1	0	0

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

Electrocardiograms

Table 41 Summary of *Electrocardiograms QTcF values (SAF)*

	Darolutamide (N=445)			Placebo (N=221)		
Category	**Baseline (N=444)**	**EOT (N=111)**	**Last visit (N=445)**	**Baseline (N=221)**	**EOT (N=98)**	**Last visit (N=221)**
Value ≤450 msec	403 (90.8)	99 (89.2)	385 (86.5)	201 (91.0)	88 (89.8)	196 (88.7)
Value >450 to 480 msec	32 (7.2)	11 (9.9)	49 (11.0)	14 (6.3)	9 (9.2)	21 (9.5)
Value >480 to 500 msec	3 (0.7)	0	4 (0.9)	4 (1.8)	1 (1.0)	4 (1.8)
Value >500 msec	6 (1.4)	1 (0.9)	7 (1.6)	2 (0.9)	0	0
Increase >30 to 60 msec from baseline	NA	8 (7.2)	45 (10.1)	NA	5 (5.1)	20 (9.0)
Increase >60 msec from baseline	NA	0	13 (2.9)	NA	1 (1.0)	5 (2.3)

EOT=End of treatment; N=Total number of participants; n=Number of participants with event; NA=Not applicable; QTcF=Corrected QT (Fridericia's formulae)

Seven participants had a postbaseline QTcF value >500 msec at the last study visit, but 2 of these 7 participants are among the 6 participants who had baseline QTcF value >500 msec.

The TEAE ECG QT prolonged was reported in 5 participants (1.1%) in the darolutamide arm and in 3 participants (1.4%) in the placebo arm. All of these TEAEs of ECG QT prolonged were reported as nonserious and did not results in any study drug dosing modifications.

Safety in special populations

Age

ARANOTE

Table 42 TEAEs experienced by ⩾5% of participants in either treatment arm by age group- ARANOTE (SAF)

Number (%) of participants	Darolutamide				Placebo			
Age group:	<65 yrs N=117	65-74 yrs N=193	75-84 yrs N=117	≥85 yrs N=18	<65 yrs N=64	65-74 yrs N=95	75-84 yrs N=52	≥85 yrs N=10
Any TEAE	106 (90.6)	172 (89.1)	111 (94.9)	16 (88.9)	54 (84.4)	87 (91.6)	48 (92.3)	10 (100.0)
Anaemia	23 (19.7)	35 (18.1)	30 (25.6)	3 (16.7)	8 (12.5)	22 (23.2)	5 (9.6)	4 (40.0)
Arthralgia	17 (14.5)	16 (8.3)	21 (17.9)	1 (5.6)	6 (9.4)	13 (13.7)	5 (9.6)	1 (10.0)
Urinary tract infection	10 (8.5)	18 (9.3)	22 (18.8)	2 (11.1)	6 (9.4)	4 (4.2)	5 (9.6)	2 (20.0)
Aspartate aminotransferase increased	12 (10.3)	18 (9.3)	12 (10.3)	1 (5.6)	5 (7.8)	10 (10.5)	2 (3.8)	0
Back pain	14 (12.0)	18 (9.3)	10 (8.5)	1 (5.6)	8 (12.5)	8 (8.4)	7 (13.5)	0
Constipation	6 (5.1)	16 (8.3)	17 (14.5)	3 (16.7)	7 (10.9)	5 (5.3)	2 (3.8)	2 (20.0)
Hot flush	13 (11.1)	17 (8.8)	9 (7.7)	2 (11.1)	2 (3.1)	12 (12.6)	2 (3.8)	0
Alanine aminotransferase increased	12 (10.3)	16 (8.3)	11 (9.4)	1 (5.6)	7 (10.9)	10 (10.5)	1 (1.9)	0
Hypertension	13 (11.1)	13 (6.7)	10 (8.5)	2 (11.1)	4 (6.3)	11 (11.6)	3 (5.8)	1 (10.0)
Pain in extremity	14 (12.0)	14 (7.3)	10 (8.5)	0	9 (14.1)	10 (10.5)	1 (1.9)	0
Bone pain	11 (9.4)	11 (5.7)	10 (8.5)	1 (5.6)	5 (7.8)	15 (15.8)	6 (11.5)	1 (10.0)
Weight increased	9 (7.7)	13 (6.7)	10 (8.5)	1 (5.6)	3 (4.7)	9 (9.5)	5 (9.6)	0
COVID-19	6 (5.1)	13 (6.7)	10 (8.5)	3 (16.7)	4 (6.3)	5 (5.3)	4 (7.7)	2 (20.0)
Blood alkaline phosphatase increased	11 (9.4)	12 (6.2)	7 (6.0)	0	4 (6.3)	7 (7.4)	2 (3.8)	0
Insomnia	6 (5.1)	10 (5.2)	12 (10.3)	0	1 (1.6)	3 (3.2)	2 (3.8)	0
Hyperglycaemia	8 (6.8)	9 (4.7)	8 (6.8)	2 (11.1)	1 (1.6)	5 (5.3)	1 (1.9)	1 (10.0)
Fatigue	3 (2.6)	11 (5.7)	8 (6.8)	3 (16.7)	4 (6.3)	10 (10.5)	4 (7.7)	0
Blood creatinine increased	5 (4.3)	9 (4.7)	6 (5.1)	1 (5.6)	1 (1.6)	9 (9.5)	4 (7.7)	1 (10.0)
Headache	5 (4.3)	8 (4.1)	5 (4.3)	0	5 (7.8)	6 (6.3)	2 (3.8)	1 (10.0)

COVID-19=Coronavirus disease 2019; CTCAE=Common Terminology Criteria for Adverse Events; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of participants (100%); SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: The most common TEAEs by MedDRA PT occurring in ≥5% of participants in either treatment arm overall are presented.
CTCAE Version 5.0 and MedDRA Version 27.0.

ARANOTE+ARAMIS pool

Results for the ARANOTE+ARAMIS pool were generally similar to those for ARANOTE.

For participants in the various age subgroups, individual TEAEs, with a ≥5 percentage point higher incidence, and EAIRs, with ≥1 event per 100 PY higher, in the darolutamide arm compared with the placebo arm are listed below:

- Aged <65 years: back pain
- Aged 65 to 74 years: none
- Aged 75 to 84 years: none
- Aged ≥85 years: constipation and fatigue

Geographical region

ARANOTE

Table 43 TEAEs experienced by ⩾5% of participants in either treatment arm by geographic region-ARANOTE (SAF)

Number (%) of participants	Darolutamide			Placebo		
Geographical region:	Europe/ ROW N=184	Asia N=141	Latin Am. N=120	Europe/ ROW N=88	Asia N=63	Latin Am. N=70
Any TEAE	155 (84.2)	133 (94.3)	117 (97.5)	74 (84.1)	57 (90.5)	68 (97.1)
Anaemia	28 (15.2)	31 (22.0)	32 (26.7)	10 (11.4)	9 (14.3)	20 (28.6)
Arthralgia	18 (9.8)	18 (12.8)	19 (15.8)	4 (4.5)	8 (12.7)	13 (18.6)
Urinary tract infection	14 (7.6)	22 (15.6)	16 (13.3)	5 (5.7)	7 (11.1)	5 (7.1)
Aspartate aminotransferase increased	11 (6.0)	11 (7.8)	21 (17.5)	2 (2.3)	7 (11.1)	8 (11.4)
Back pain	9 (4.9)	18 (12.8)	16 (13.3)	8 (9.1)	4 (6.3)	11 (15.7)
Constipation	9 (4.9)	18 (12.8)	15 (12.5)	5 (5.7)	7 (11.1)	4 (5.7)
Hot flush	21 (11.4)	2 (1.4)	18 (15.0)	7 (8.0)	1 (1.6)	8 (11.4)
Alanine aminotransferase increased	9 (4.9)	13 (9.2)	18 (15.0)	4 (4.5)	6 (9.5)	8 (11.4)
Hypertension	12 (6.5)	12 (8.5)	14 (11.7)	6 (6.8)	4 (6.3)	9 (12.9)
Pain in extremity	10 (5.4)	18 (12.8)	10 (8.3)	6 (6.8)	10 (15.9)	4 (5.7)
Bone pain	11 (6.0)	5 (3.5)	17 (14.2)	8 (9.1)	4 (6.3)	15 (21.4)
Weight increased	7 (3.8)	25 (17.7)	1 (0.8)	6 (6.8)	10 (15.9)	1 (1.4)
COVID-19	17 (9.2)	10 (7.1)	5 (4.2)	7 (8.0)	5 (7.9)	3 (4.3)
Blood alkaline phosphatase increased	6 (3.3)	7 (5.0)	17 (14.2)	1 (1.1)	2 (3.2)	10 (14.3)
Insomnia	9 (4.9)	8 (5.7)	11 (9.2)	1 (1.1)	1 (1.6)	4 (5.7)
Hyperglycaemia	3 (1.6)	10 (7.1)	14 (11.7)	1 (1.1)	3 (4.8)	4 (5.7)
Fatigue	14 (7.6)	4 (2.8)	7 (5.8)	10 (11.4)	2 (3.2)	6 (8.6)
Blood creatinine increased	4 (2.2)	6 (4.3)	11 (9.2)	5 (5.7)	4 (6.3)	6 (8.6)
Headache	9 (4.9)	4 (2.8)	5 (4.2)	6 (6.8)	2 (3.2)	6 (8.6)

Am.=America; COVID-19=Coronavirus diseae 2019; CTCAE=Common Terminology Criteria for Adverse Events; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; Impair.=Impairment; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of participants (100%); ROW=Rest of the world; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: The most common TEAEs by MedDRA PT occurring in ≥5% of participants overall in either treatment arm are presented.

CTCAE Version 5.0 and MedDRA Version 27.0

ARANOTE+ARAMIS pool

No meaningful conclusion can be drawn due to the different regions that participated in the 2 studies included in the pool.

Renal function at baseline

ARANOTE

Table 44 TEAEs experienced by ⩾5% of participants in either treatment arm by renal function at baseline-ARANOTE (SAF)

Number (%) of participants	Darolutamide			Placebo		
Renal function (eGFR at baseline)	Normal N=221	Mild Impair. N=178	Moderate Impair. N=45	Normal N=102	Mild Impair. N=91	Moderate Impair. N=27
Any TEAE	209 (94.6)	155 (87.1)	40 (88.9)	92 (90.2)	82 (90.1)	24 (88.9)
Anaemia	51 (23.1)	28 (15.7)	12 (26.7)	14 (13.7)	19 (20.9)	6 (22.2)
Arthralgia	25 (11.3)	21 (11.8)	8 (17.8)	11 (10.8)	11 (12.1)	3 (11.1)
Urinary tract infection	21 (9.5)	22 (12.4)	8 (17.8)	5 (4.9)	9 (9.9)	3 (11.1)
Aspartate aminotransferase increased	21 (9.5)	19 (10.7)	3 (6.7)	11 (10.8)	6 (6.6)	0
Back pain	21 (9.5)	19 (10.7)	3 (6.7)	9 (8.8)	11 (12.1)	3 (11.1)
Constipation	21 (9.5)	14 (7.9)	7 (15.6)	6 (5.9)	8 (8.8)	2 (7.4)
Hot flush	22 (10.0)	15 (8.4)	3 (6.7)	11 (10.8)	3 (3.3)	2 (7.4)
Alanine aminotransferase increased	19 (8.6)	18 (10.1)	3 (6.7)	7 (6.9)	10 (11.0)	1 (3.7)
Hypertension	23 (10.4)	12 (6.7)	3 (6.7)	8 (7.8)	7 (7.7)	3 (11.1)
Pain in extremity	21 (9.5)	12 (6.7)	5 (11.1)	6 (5.9)	10 (11.0)	3 (11.1)
Bone pain	20 (9.0)	12 (6.7)	1 (2.2)	13 (12.7)	10 (11.0)	4 (14.8)
Weight increased	21 (9.5)	9 (5.1)	3 (6.7)	9 (8.8)	6 (6.6)	2 (7.4)
COVID-19	16 (7.2)	12 (6.7)	4 (8.9)	8 (7.8)	6 (6.6)	1 (3.7)
Blood alkaline phosphatase increased	17 (7.7)	11 (6.2)	2 (4.4)	7 (6.9)	6 (6.6)	0
Insomnia	13 (5.9)	12 (6.7)	2 (4.4)	4 (3.9)	0	1 (3.7)
Hyperglycaemia	17 (7.7)	9 (5.1)	1 (2.2)	5 (4.9)	2 (2.2)	1 (3.7)
Fatigue	12 (5.4)	12 (6.7)	0	6 (5.9)	7 (7.7)	4 (14.8)
Blood creatinine increased	5 (2.3)	9 (5.1)	7 (15.6)	0	7 (7.7)	7 (25.9)
Headache	11 (5.0)	6 (3.4)	1 (2.2)	8 (7.8)	5 (5.5)	1 (3.7)

COVID-19=Coronavirus disease 2019; CTCAE=Common Terminology Criteria for Adverse Events; eGFR=Estimated glomerular filtration rate; Impair.=Impairment; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of participants (100%); SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: The most common TEAEs by MedDRA PT occurring in ≥5% of participants in either treatment arm are presented.

CTCAE Version 5.0 and MedDRA Version 27.0.

ARANOTE+ARAMIS pool

Results for the ARANOTE+ARAMIS pool were generally similar to those for ARANOTE, except that the darolutamide arm had a higher incidence (by ≥5 percentage points) of study drug-related TEAEs than for the placebo arm for participants with moderate impairment of renal function at baseline.

Across the baseline renal function subgroups, incidences of individual TEAEs were comparable between the darolutamide and placebo arms.

Hepatic function at baseline

ARANOTE

Table 45 TEAEs experienced by ⩾5% of participants in either treatment arm by hepatic function at baseline-ARANOTE (SAF)

Number (%) of participants	Darolutamide		Placebo	
Hepatic function at baseline:	Normal N=387	Mild Impair. N=58	Normal N=202	Mild Impair. N=19
Any TEAE	351 (90.7)	54 (93.1)	183 (90.6)	16 (84.2)
Anaemia	75 (19.4)	16 (27.6)	36 (17.8)	3 (15.8)
Arthralgia	47 (12.1)	8 (13.8)	24 (11.9)	1 (5.3)
Urinary tract infection	44 (11.4)	8 (13.8)	15 (7.4)	2 (10.5)
Aspartate aminotransferase increased	31 (8.0)	12 (20.7)	17 (8.4)	0
Back pain	40 (10.3)	3 (5.2)	22 (10.9)	1 (5.3)
Constipation	37 (9.6)	5 (8.6)	15 (7.4)	1 (5.3)
Hot flush	37 (9.6)	4 (6.9)	15 (7.4)	1 (5.3)
Alanine aminotransferase increased	27 (7.0)	13 (22.4)	18 (8.9)	0
Hypertension	32 (8.3)	6 (10.3)	17 (8.4)	2 (10.5)
Pain in extremity	35 (9.0)	3 (5.2)	19 (9.4)	1 (5.3)
Bone pain	29 (7.5)	4 (6.9)	24 (11.9)	3 (15.8)
Weight increased	25 (6.5)	8 (13.8)	16 (7.9)	1 (5.3)
COVID-19	28 (7.2)	4 (6.9)	14 (6.9)	1 (5.3)
Blood alkaline phosphatase increased	26 (6.7)	4 (6.9)	12 (5.9)	1 (5.3)
Insomnia	27 (7.0)	1 (1.7)	6 (3.0)	0
Hyperglycaemia	23 (5.9)	4 (6.9)	8 (4.0)	0
Fatigue	20 (5.2)	5 (8.6)	18 (8.9)	0
Blood creatinine increased	18 (4.7)	3 (5.2)	15 (7.4)	0
Headache	16 (4.1)	2 (3.4)	11 (5.4)	3 (15.8)

COVID-19=Coronavirus diease 2019; CTCAE=Common Terminology Criteria for Adverse Events; Impair.=Impairment; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of participants (100%); SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: The most common TEAEs by MedDRA PT occurring in ≥5% of participants overall in either treatment arm are presented.

CTCAE Version 5.0 and MedDRA Version 27.0.

ARANOTE+ARAMIS pool

Results for the ARANOTE+ARAMIS pool were generally similar to those for ARANOTE.

For participants with mild hepatic impairment at baseline, the TEAEs observed with a ≥5 percentage point higher incidence and EAIRs with ≥1 event per 100 PY higher in the darolutamide arm compared with the placebo arm were as follows (darolutamide vs placebo):

- Constipation: 7.5% vs 1.6% (EAIRs: 5.2 vs 1.4)
- ALT increased: 9.6% vs 0% (EAIRs: 6.9 vs 0)
- AST increased: 9.6% vs 0% (EAIRs: 6.8 vs 0)
- Arthralgia: 8.2% vs 1.6% (EAIRs: 5.7 vs 1.4)
- Hot flush: 8.9% vs 1.6% (EAIRs: 6.4 vs 1.4)

For these events, the imbalances were due to Grade 1 and Grade 2 events.

ECOG performance status at baseline

ARANOTE

Table 46: TEAEs experienced by ⩾5% of participants in either treatment arm by ECOG PS at baseline-ARANOTE (SAF)

Number (%) of participants ECOG PS at baseline:	Darolutamide 0 N=235	Darolutamide ≥1 N=210	Placebo 0 N=96	Placebo ≥1 N=125
Any TEAE	211 (89.8)	194 (92.4)	87 (90.6)	112 (89.6)
Anaemia	45 (19.1)	46 (21.9)	16 (16.7)	23 (18.4)
Arthralgia	24 (10.2)	31 (14.8)	8 (8.3)	17 (13.6)
Urinary tract infection	19 (8.1)	33 (15.7)	9 (9.4)	8 (6.4)
Aspartate aminotransferase increased	27 (11.5)	16 (7.6)	11 (11.5)	6 (4.8)
Back pain	27 (11.5)	16 (7.6)	15 (15.6)	8 (6.4)
Constipation	21 (8.9)	21 (10.0)	6 (6.3)	10 (8.0)
Hot flush	32 (13.6)	9 (4.3)	9 (9.4)	7 (5.6)
Alanine aminotransferase increased	24 (10.2)	16 (7.6)	12 (12.5)	6 (4.8)
Hypertension	23 (9.8)	15 (7.1)	10 (10.4)	9 (7.2)
Pain in extremity	17 (7.2)	21 (10.0)	9 (9.4)	11 (8.8)
Bone pain	21 (8.9)	12 (5.7)	11 (11.5)	16 (12.8)
Weight increased	16 (6.8)	17 (8.1)	7 (7.3)	10 (8.0)
COVID-19	19 (8.1)	13 (6.2)	8 (8.3)	7 (5.6)
Blood alkaline phosphatase increased	17 (7.2)	13 (6.2)	6 (6.3)	7 (5.6)
Insomnia	14 (6.0)	14 (6.7)	6 (6.3)	0
Hyperglycaemia	16 (6.8)	11 (5.2)	2 (2.1)	6 (4.8)
Fatigue	15 (6.4)	10 (4.8)	11 (11.5)	7 (5.6)
Blood creatinine increased	10 (4.3)	11 (5.2)	7 (7.3)	8 (6.4)
Headache	9 (3.8)	9 (4.3)	5 (5.2)	9 (7.2)

COVID-19=Coronavirus disease 2019; CTCAE=Common Terminology Criteria for Adverse Events; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of participants (100%); SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: The most common TEAEs by MedDRA PT occurring in ≥5% of participants overall in either treatment arm are presented.

CTCAE Version 5.0 and MedDRA Version 27.0

ARANOTE+ARAMIS pool

The results of the ARANOTE+ARAMIS pool were generally similar with the results of ARANOTE.

Additional safety analyses from ongoing Study 20321 (ROS)

As of the database cut-off date of 30 JAN 2024, 676 participants have been enrolled in Study ROS 20321, with 286 participants still taking OL darolutamide.

Deaths

Table 47 Fatal TEAEs in ROS Study

Event (MedDRA PT)	Number of events
Death	3
Acute coronary syndrome	1
Acute kidney injury	1
Aortic rupture	1
Bladder cancer	1
Cardiac failure	1
Cardiopulmonary failure	1
Cerebral haematoma	1
Cerebrovascular accident	1
H1N1 influenza	1
Marasmus	1
Mesothelioma	1
Myocardial ischaemia	1
Nosocomial infection	1
Pancytopenia	1
Pneumonia	1
Pneumonia viral	1
Post procedural pneumonia	1
Prostate cancer metastatic	1
Respiratory failure	1
Road traffic accident	1
Sepsis	1
Spinal cord injury cervical	1
Total	**25 events in 24 (3.55%) participants**

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; ROS=roll-over study; TEAE=treatment-emergent adverse event

Note: As of the database cut-off date of 30 JAN 2024, 676 participants have been enrolled in this ROS and 286 are still taking open-label darolutamide

SAEs

As of the database cut-off date (30 JAN 2024), at least 1 SAE was reported in 129 (19.1%) out of 676 participants during treatment with darolutamide in addition to ADT or within 30 days after study treatment discontinuation in Study 20321. Overall, a total of 217 SAEs have been reported during the conduct of Study 20321.

SAEs were most frequently reported (≥5%) in the SOCs Infections and infestations (48 events), Renal and urinary disorders (33 events), Cardiac disorders (23 events), Gastrointestinal disorders (17 events), Nervous system disorders (17 events), Injury, poisoning and procedural complications (14 events), and Neoplasms benign, malignant and unspecified (12 events). The most common SAEs (≥2%; reported 5 or more times) included pneumonia, haematuria, acute kidney injury, small intestinal obstruction, COVID-19 pneumonia, and urinary tract infection. Small intestinal obstruction was confounded by pre-existing risk factors, including a medical history of contributory conditions (Barrett's oesophagus and diverticulitis) or surgery (colectomy). Pneumonia and COVID-19 pneumonia are associated with an infectious process of viral origin occurring during a global pandemic.

The remaining TEAEs are signs or symptoms of complications associated with underlying prostate cancer. Notably, all events in the SOC of Cardiac disorders were reported <5 times (<2%). Excluding fatal events, 12 SAEs in 11 participants resulted in discontinuation of the study drug and included lymphadenopathy (2 events) and 1 event each of adenocarcinoma of the colon, cerebrovascular accident, COVID-19, failure to thrive, haemorrhagic stroke, hypoxia, left ventricular dysfunction, pneumonia, small cell lung cancer, and urinary tract obstruction. None of the events resulting in discontinuation of darolutamide were considered related to the study drug by the investigator.

Discontinuation due to adverse events

Table 48 TEAEs experienced by ⩾ 2% of participants in either treatment arm that led to darolutamide/placebo permanent discontinuation (SAF)

	ARANOTE				ARANOTE+ARAMIS			
	Darolutamide (N=445)		Placebo (N=221)		Darolutamide (N=1399)		Placebo (N=775)	
Preferred term	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Alanine aminotransferase increased	2 (0.4)	0.2	1 (0.5)	0.3	2 (0.1)	0.1	1 (0.1)	0.1
Aspartate aminotransferase increased	2 (0.4)	0.2	1 (0.5)	0.3	3 (0.2)	0.1	1 (0.1)	0.1
Craniocerebral injury	2 (0.4)	0.2	0	0	2 (0.1)	0.1	0	0
Myocardial infarction	2 (0.4)	0.2	0	0	3 (0.2)	0.1	1 (0.1)	0.1
Back pain	0	0	2 (0.9)	0.6	0	0	2 (0.3)	0.2
Gastrointestinal haemorrhage	0	0	2 (0.9)	0.6	0	0	2 (0.3)	0.2
Pain in extremity	0	0	2 (0.9)	0.6	0	0	2 (0.3)	0.2
Cardiac arrest	0	0	1 (0.5)	0.3	2 (0.1)	0.1	3 (0.4)	0.3
Cardiac failure	0	0	0	0	4 (0.3)	0.2	4 (0.5)	0.4
Abdominal pain	0	0	0	0	2 (0.1)	0.1	0	0
Diarrhoea	0	0	0	0	2 (0.1)	0.1	0	0
Death	0	0	1 (0.5)	0.3	4 (0.3)	0.2	2 (0.3)	0.2
General physical health deterioration	0	0	0	0	2 (0.1)	0.1	0	0
Pneumonia	1 (0.2)	0.1	0	0	4 (0.3)	0.2	0	0
Blood creatinine increased	1 (0.2)	0.1	0	0	3 (0.2)	0.1	0	0
Bone pain	1 (0.2)	0.1	1 (0.5)	0.3	2 (0.1)	0.1	1 (0.1)	0.1
Diffuse large B-cell lymphoma	1 (0.2)	0.1	0	0	2 (0.1)	0.1	0	0

Pancreatic carcinoma	0	0	0	0	2 (0.1)	0.1	0	0
Cerebral infarction	0	0	1 (0.5)	0.3	2 (0.1)	0.1	1 (0.1)	0.1
Cerebrovascular accident	0	0	0	0	0	0	2 (0.3)	0.2
Ischaemic stroke	0	0	0	0	2 (0.1)	0.1	2 (0.3)	0.2
Urinary retention	1 (0.2)	0.1	0	0	2 (0.1)	0.1	0	0
Acute respiratory failure	0	0	0	0	1 (<0.1)	<0.1	2 (0.3)	0.2
Pulmonary embolism	0	0	1 (0.5)	0.3	2 (0.1)	0.1	2 (0.3)	0.2
Hypertension	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	2 (0.3)	0.2

EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants; n=Number of participants with at least one row event; PY=Participant years; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Note: Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.

EAIR=number of participants with the event / sum of exposure times, where exposure time is time to first occurrence if an event occurred, otherwise it is treatment duration and time at risk after treatment end, where time at risk after treatment end = time after end of treatment up to minimum of death date, data cut-off, open-label start, end of treatment-emergent window, lost to follow-up. For ARANOTE, withdrawal from study is also considered.

MedDRA Version 27.0.

TEAEs leading to dose interruption

Table 49 TEAEs experienced by ⩾ 0.5% of participants in either treatment arm that led to dose interruption (SAF)

	ARANOTE Darolutamide N=445		ARANOTE Placebo N=221		ARANOTE+ARAMIS Darolutamide N=1399		ARANOTE+ARAMIS Placebo N=775	
Preferred term	**n (%)**	**EAIR / 100 PY**	**n (%)**	**EAIR / 100 PY**	**n (%)**	**EAIR / 100 PY**	**n (%)**	**EAIR / 100 PY**
Hypertension	4 (0.9)	0.5	1 (0.5)	0.3	10 (0.7)	0.5	1 (0.1)	0.1
Aspartate aminotransferase increased	7 (1.6)	0.9	1 (0.5)	0.3	9 (0.6)	0.4	1 (0.1)	0.1
Pneumonia	2 (0.4)	0.2	0	0	8 (0.6)	0.4	2 (0.3)	0.2
Alanine aminotransferase increased	6 (1.3)	0.8	1 (0.5)	0.3	7 (0.5)	0.3	1 (0.1)	0.1
Diarrhoea	2 (0.4)	0.2	0	0	7 (0.5)	0.3	1 (0.1)	0.1
Anaemia	4 (0.9)	0.5	1 (0.5)	0.3	6 (0.4)	0.3	1 (0.1)	0.1
Rash	4 (0.9)	0.5	1 (0.5)	0.3	5 (0.4)	0.2	1 (0.1)	0.1
Hepatic function abnormal	3 (0.7)	0.4	0	0	4 (0.3)	0.2	0	0
Urinary tract infection	4 (0.9)	0.5	0	0	4 (0.3)	0.2	0	0
COVID-19	3 (0.7)	0.4	1 (0.5)	0.3	3 (0.2)	0.1	1 (0.1)	0.1
Urinary retention	1 (0.2)	0.1	0	0	2 (0.1)	0.1	5 (0.6)	0.5

EAIR=exposure-adjusted incidence rate, MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants, n=number of participants with at least 1 event; PY=Participant year; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

Note: EAIR = number of participants with the event / sum of exposure times, where exposure time is time to first occurrence if an event occurred, otherwise it is treatment duration and time at risk after treatment end, where time at risk after treatment end = time after end of treatment up to minimum of death date, data cut-off, open-label start, end of treatment-emergent window, lost to follow-up. For ARANOTE, withdrawal from study is also considered.
MedDRA Version 27.0.
Percentages are calculated relative to the respective treatment group. Participants may be counted in more than 1 row.
The selection is based on unrounded percentage values.

TEAEs leading to dose reduction

Table 50 All TEAEs that led to dose reduction in ARANOTE and TEAEs that led to dose reduction in ⩾ 2 % participants in either treatment arm in the ARANOTE+ARAMIS pool (SAF)

	ARANOTE				ARANOTE+ARAMIS			
	Darolutamide (N=445)		Placebo (N=221)		Darolutamide (N=1399)		Placebo (N=775)	
Preferred term	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Aspartate aminotransferase increased	3 (0.7)	0.4	1 (0.5)	0.3	4 (0.3)	0.2	1 (0.1)	0.1
Alanine aminotransferase increased	2 (0.4)	0.2	1 (0.5)	0.3	2 (0.1)	0.1	1 (0.1)	0.1
Hypertension	2 (0.4)	0.2	1 (0.5)	0.3	4 (0.3)	0.2	2 (0.3)	0.2
Rash	2 (0.4)	0.3	0	0	3 (0.2)	0.1	0	0
Abdominal pain upper	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Anaemia	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Arthralgia	1 (0.2)	0.1	0	0	2 (0.1)	0.1	0	0
Blood creatinine increased	1 (0.2)	0.1	0	0	3 (0.2)	0.1	0	0
Blood urea increased	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Hepatic function abnormal	1 (0.2)	0.1	0	0	2 (0.1)	0.1	1 (0.1)	0.1
Hypokalaemia	1 (0.2)	0.1	0	0	2 (0.1)	0.1	0	0
Leukopenia	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Neutropenia	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Platelet count decreased	1 (0.2)	0.1	0	0	2 (0.1)	0.1	0	0
Rash papular	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Thrombocytopenia	1 (0.2)	0.1	0	0	1 (<0.1)	<0.1	0	0
Gastritis	0	0	1 (0.5)	0.3	0	0	1 (0.1)	0.1
Fatigue	0	0	0	0	7 (0.5)	0.3	2 (0.3)	0.2
Decreased appetite	0	0	0	0	2 (0.1)	0.1	0	0
Renal impairment	0	0	0	0	2 (0.1)	0.1	0	0
Hot flush	0	0	0	0	2 (0.1)	0.1	0	0

EAIR=Exposure-adjusted incidence rate; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants; n=Number of participants with at least one row event; PY=participant years; SAF=safety analysis set; TEAE=Treatment-emergent adverse event

Note: Percentages are calculated relative to the respective treatment arm. Participants may be counted in more than one row.

EAIR= number of participants with the event / sum of exposure times, where exposure time is time to first occurrence if an event occurred, otherwise it is treatment duration and time at risk after treatment end, where time at risk after treatment end = time after end of treatment up to minimum of death date, data cut-off, open-label start, end of treatment-emergent window, lost to follow-up. For ARANOTE, withdrawal from study is also considered.

MedDRA Version 27.0.

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 (30 JAN 2024).

2.5.1. Discussion on clinical safety

The safety data of darolutamide in the proposed indication are based mainly on the Phase 3 Study ARANOTE in mHSPC participants. Supportive safety data are derived from the Phase 3 Study ARAMIS in non-metastatic castration resistance prostate cancer (nmCRPC), as part of the pooled analysis and Study 20321 ROS for the long-term safety of darolutamide. This database is considered suitable for characterisation of the safety profile of darolutamide for the claimed indication in its general aspects.

The safety profile of darolutamide as presented in the SmPC section 4.8 derived from the pool safety analysis of ARANOTE+ARAMIS which were generally similar with the results of ARANOTE.

In ARANOTE study, a total of 669 patients were randomized to receive darolutamide or placebo concurrently with ADT in a 2:1 ratio. As of the database cut-off date for the primary completion analysis (07 JUN 2024), the median time of treatment was longer in the darolutamide arm than in the placebo

arm (24.2 vs 17.3 months, respectively). The median percentage of the planned dose received was 100% for both treatment arms. In the ARANOTE +ARAMIS pool, the treatment duration was longer in the darolutamide arm than in the placebo arm (medians: 18.2 vs 11.6 months, respectively). More than half of the patients in the darolutamide arm (50.3% darolutamide vs. 34.4% placebo) received treatment ≥24 months in ARANOTE study.

The number of patients in the age groups of ≥85 years was lower compared to other age groups in both arms. The demographic and baseline characteristics were well balanced between darolutamide and placebo arms in the ARANOTE study and were representative of the targeted population (mHSPC patients).

ECOG performance status at baseline was 0 or 1 in most patients in both darolutamide and placebo arms (53% and 45% vs. 44% and 52.6%, respectively).

Analysis of adverse events

In ARANOTE study, the overall proportion of treatment-emerged adverse events (TEAEs) was balanced between the darolutamide and placebo arms (91.0% and 90.1%, respectively). TEAEs that were assessed related to treatment by the investigator occurred in 32.4% of patients in the darolutamide arm and in 29% of patients in the placebo arm.

In the majority of patients, TEAEs were of CTCAE grade 1 or 2, with a similar incidence between the treatment arms (darolutamide: 55.5% vs placebo: 54.3%). TEAEs with worst grade of 3 or 4 were balanced between the treatment arms (30.8% vs 30.3%). The incidences of SAEs (23.6% vs 23.5%) and TEAEs with a fatal outcome (Grade 5) (4.7% vs 5.4%) were comparable in both treatment arms. TEAEs leading to permanent discontinuation of treatment were reported with a lower incidence in the darolutamide arm than in the placebo arm (6.1% and 9.0%, respectively). TEAEs leading to dose modifications were reported with higher incidence in darolutamide arm compared to placebo (15% vs 9%).

Common adverse events

In ARANOTE study, the most common TEAEs reported, with a higher incidence in the darolutamide arm than in the placebo arm, were anemia, urinary tract infection, AST increased, constipation, hot flush, insomnia, hyperglycemia, pneumonia, blood bilirubin increased, and hyperlipidemia. After adjusting for the difference in study treatment duration, the EAIRs per 100 PY that remained higher in the darolutamide arm than the placebo were urinary tract infection (6.8 vs 5.3, respectively), insomnia (3.6 vs 1.8), hyperglycemia (3.5 vs 2.4), pneumonia (2.0 vs 0.6), blood bilirubin increased (2.4 vs 0.6), upper respiratory tract infection (1.5 vs 0.6), AST increased (5.7 vs 5.3), blood lactate dehydrogenase increased (1.4 vs 0.6), thrombocytopenia (1.3 vs 0.9) and hyperlipidemia (1.4 vs 0.3). Results for the ARANOTE+ARAMIS pool were generally consistent with results from ARANOTE. However, some additional AEs occurred with higher incidence in darolutamide arm compared to placebo as angina pectoris (0.8 vs 0.4).

Treatment related AEs experienced by >2% of participants in the darolutamide arm were AST increased, anemia, ALT increased, weight increased, hypertension, fatigue, hot flush, and blood bilirubin increased. After adjusting for treatment duration, the incidence of TRAEs of anemia (3.1 per 100 PY vs 1.5), weight increased (2.4 vs 1.8), gamma-glutamyltransferase increased (0.6 vs 0), hypertension (1.6 vs 1.2) and platelet count decreased (0.8 vs 0.3) remained higher in the darolutamide arm than the placebo arm. These results were similar in the safety pool analysis (ARANOTE+ARAMIS).

Musculoskeletal pain: comparison of event incidences in the pooled safety analysis (ARANOTE+ARAMIS) showed a lower incidence of bone pain (3.0% vs 4.3%), back pain (9.0% vs 9.3%), and musculoskeletal pain (0.6% vs 0.8%) in the darolutamide arm compared to the placebo arm. The incidence of arthralgia

was identical in both groups (10.7%). The same conclusions were observed in the ARANOTE study. Musculoskeletal pain has been removed as ADR from section 4.8 of the SmPC for mHSPC patients treated with darolutamide in ARAMIS and ARANOTE studies.

Worst grade 3 and 4 adverse events

In ARANOTE, TEAEs with a worst grade of 3 or 4 reported with a higher incidence in the darolutamide arm than in the placebo arm were ALT increased (2% vs 0.5%), AST increased (2.2% vs 0.5%), hypertension (4.3% vs 3.6%), urinary tract infection (1.8% vs 0.5%), bone pain (2.0% vs 1.4%) and spinal cord compression (1.1% vs 0.5%).

TREAEs with a worst grade of 3 and 4 were reported with comparable incidences in the darolutamide (6.3%) and placebo arms (4.5%). The most common TREAE with a worst grade of 3 or 4 was hypertension (1.8% vs 0.5%; all events were Grade 3). Other most common grade 3 or 4 treatment-related events included AST increased (1.1% vs 0%), ALT increased (1.3% vs 0%), anemia (0.7% vs 0%), and rash (0.7% vs 0%). AST increased, ALT increased, and rash are ADRs of darolutamide. These results are supported by the safety pool analysis.

Analysis of Death

A total of 105 patients (23.6%) in the darolutamide arm and 61 patients (27.6%) in the placebo arm had died in ARANOTE study as of the data cut-off date.

Altogether, 0.4% vs. 0% of patients in the darolutamide and placebo treatment arms, respectively, had died during the study treatment period (from first to last dose of study drug). In 5.6% vs. 6.8% of patients, respectively, the death occurred within 30 days after the last dose of the study drug.

The most common cause of death in both darolutamide and placebo arms was progressive disease (13.5% vs. 18.6%).

TEAEs resulting in death (grade 5) occurred in 4.7% and 5.4% of patients in the darolutamide and placebo arms, respectively. Grade 5 TEAEs that were reported in more than 1 patient in either arm were death (0.4% vs. 0.9%), craniocerebral injury (0.4% vs 0%), myocardial infarction (0.4% vs 0%), septic shock (0.4% vs 0%) and sepsis (0.2% vs 0.5%).

In the safety pool, TEAEs with a worst Grade of 5 were reported with balanced incidence between the treatment arms (58 [4.1%] participants in the darolutamide arm and 30 [3.9%] participants in the placebo arm).

Serious adverse events (SAEs)

In ARANOTE study, TESAEs reported with a higher incidence in darolutamide arm compared to placebo arm were urinary tract infection (1.0 vs 0.3) and spinal cord compression (0.6 vs 0).

Five participants (all in the darolutamide arm) had TESAEs of spinal cord compression. 4 events were Grade 3 and 1 event was Grade 4; and 4 events required/prolonged hospitalization and 1 event led to study drug discontinuation. All 5 events were considered unrelated to treatment and occurred in the presence of confounding factors increasing the risk of fracture and resultant complications (evidence of progressive, metastatic disease including metastases in spine and concomitant medications associated with a risk of fracture secondary to osteoporosis / osteopenia including anticoagulants, prior antiandrogens, proton pump inhibitors and serotonin-norepinephrine reuptake inhibitors).

In ARANOTE, treatment related SAEs were reported with comparable incidence in the darolutamide (2.0%) and placebo arms (3.6%). Treatment related SAEs with a worst grade of 3 were reported in 1.6% of participants in the darolutamide arm (systemic inflammatory response syndrome, hepatic function abnormal, urinary tract infection, pelvic fracture, ALT increased, AST increased, bladder neck obstruction, and renal failure).

TEAEs leading to permanent discontinuation

In ARANOTE, TEAEs leading to permanent discontinuation of treatment were reported with a lower incidence in the darolutamide arm (6.1%) than the placebo arm (9.0%). However, TEAEs leading to dose interruption/dose reduction were reported at a higher incidence in the darolutamide arm (13.7% / 3.6%) than the placebo arm (8.6% / 1.4%). The most frequent TEAEs leading to permanent discontinuation were ALT increased (0.2 vs 0.3 per 100 PY), AST increased (0.2 vs 0.3 per 100 PY), craniocerebral injury (0.2 vs 0 per 100 PY) and myocardial infarction (0.2 vs 0 per 100 PY).

The most common TEAEs leading to interruption of the study drug were AST increased (0.9 vs 0.3 per 100 PY), ALT increased (0.8 vs 0.3 per 100 PY), hypertension (0.5 vs 0.3 per 100 PY), diarrhoea (0.2 vs 0 per 100 PY), anaemia (0.5 vs 0.3 per 100 PY), rash (0.5 vs 0.3 per 100 PY), hepatic function abnormal (0.4 vs 0 per 100 PY) and urinary tract infection (0.5 vs 0 per 100 PY). In the ARANOTE+ARAMIS pool, the most frequent TEAE leading to dose interruption in the darolutamide arm was hypertension (0.5 vs 0.1 per 100 PY).

In ARANOTE study, the most frequent TEAE leading to dose reduction in the darolutamide arm was AST increase (0.7% vs 0.5%). In the ARANOTE+ARAMIS pool, the most frequent TEAE leading to dose reduction in the darolutamide arm was fatigue (0.5% vs 0.3%).

Safety in special populations

Age: In ARANOTE study, the number of patients in both darolutamide and placebo arms, respectively, was lower in the age group of ≥85 years (N=18 and N=10) compared to the other age groups. The incidences of grade 5 TEAEs, SAEs, and TEAEs leading to permanent discontinuation of treatment were higher in the elderly age groups in both darolutamide and placebo treatment arms. No clear conclusion could be drawn due to the low number of elderly patients in both arms.

Geographic regions: There was a higher incidence in the darolutamide arm than in the placebo arm for treatment related AEs and SAEs in Asia, and for Grade 3 or 4 TEAEs and TEAEs leading to study drug dose modification in Latin America.

Of note, in Latin America subgroup, the incidences of anaemia, arthralgia, AST increased, ALT increased, hypertension, bone pain, hyperglycemia and blood creatinine increased were higher in darolutamide arm compared to Europe/ ROW group. Pain increased and weight increased were higher in darolutamide arm in Asia subgroup compared to Europe/ ROW group. However, no meaningful conclusion can be drawn from these observations.

In Asia subgroup, the incidences of serious TAEs, TEAEs leading to permanent discontinuation of treatment are higher in darolutamide arm compared to Latin America subgroup and Europe/ROW subgroup: 30% vs 19% vs 21% and 8.4% and 6 and 4% respectively. AEs of worst grade 3, 4, or 5 were higher in darolutamide arm in Asia (41%) and Latin America subgroups (40%) compared to Europe/ROW subgroup (28%). However, no meaningful conclusion can be drawn from these observations

Renal function at baseline

There were no patients with severe renal function at baseline.

Moderately impaired renal function patients (N=45) were less represented than other renal function groups in the presented dataset. Higher incidences of grade 3, 4 and 5 TEAEs, SAEs and TEAEs leading to treatment discontinuation were observed in both treatment and placebo arms.

Hepatic impairment

Patients with moderate or severe hepatic impairment are not represented in ARANOTE study. The number of participants with mild impairment of hepatic function at baseline was relatively low (N=58 and N=19 in the darolutamide and placebo arms, respectively). However, anemia (28% vs 19%), AST increased (21%

vs 8%), ALT increased (22% vs 7%), and weight increased (14% vs 7%), occurred more commonly in the darolutamide arm for patients with mildly impaired hepatic function than in patients with normal liver function. Results for the safety pool were generally similar to those of ARANOTE. All TEAEs of anemia, ALT increased and AST increased occurring in darolutamide participants with mildly impaired hepatic function were nonserious, mostly of mild severity Grades 1 and 2, no Grade 4 or 5 events occurred and none resulted in permanent discontinuation of darolutamide.

ECOG PS

TEAEs of urinary tract infection, and arthralgia had a higher incidence in the ECOG PS ≥1 subgroup, compared to ECOG PS=0 in darolutamide arm. In both treatment arms, the incidences of TEAEs leading to treatment discontinuation and serious AEs were higher in the ECOG PS ≥1 subgroup than in the ECOG PS 0 subgroup.

Additional safety analyses from ongoing Study 20321 (ROS)

Up to the DCO date for the submission (30 JAN 2024), 25 events with a fatal outcome were retrieved for participants enrolled in study 20321. None of the events with a fatal outcome was considered related to the study drug by the investigator. The most common SAEs included pneumonia, hematuria, acute kidney injury, small intestinal obstruction, COVID-19 pneumonia, and urinary tract infection.

Laboratory findings

In ARANOTE Study, the differences between the treatment arms in laboratory abnormalities were consistent with the known safety profile of darolutamide for ALT increased, AST increased, blood bilirubin increased, and neutrophil count decreased. ECG QT prolonged AE was reported in 5 participants (1.1%) in the darolutamide arm and in 3 participants (1.4%) in the placebo arm. All TEAEs of ECG QT prolonged were reported as non-serious and did not result in any study drug dosing modifications. The SmPC includes a warning that ADT may prolong the QT interval.

Neutrophil count decreased

Neutrophil count decreased was reported as a laboratory abnormality in 17.3% of patients treated with darolutamide and in 7.4% of patients treated with placebo. The median time to nadir was 225 days. The laboratory tests abnormalities manifested predominantly as grade 1 or 2 intensity. Neutrophil count decreased of grade 3 and 4 was reported in 2.6% and 0.3% of patients, respectively. Only one patient permanently discontinued darolutamide due to neutropenia. Neutropenia was either transient or reversible (83% of patients) and were not associated with any clinically relevant signs or symptoms.

Blood bilirubin increased

Bilirubin increased was reported as a laboratory abnormality in 16.1% of patients treated with darolutamide and in 6.1% of patients treated with placebo. The episodes were predominantly of grade 1 or 2 intensity, not associated with any clinically relevant signs or symptoms, and reversible after darolutamide was discontinued. Bilirubin increased of grade 3 and 4 was reported in 0.2% of patients treated with darolutamide and in 0% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased bilirubin was 187 days, and the mean duration of the first episode was 172 days. One patient was discontinued from treatment due to increase in bilirubin.

ALT and AST increased

ALT increased was reported as a laboratory abnormality in 13.3% of patients treated with darolutamide and in 9.7% of patients treated with placebo. AST increased was reported as a laboratory abnormality in 22.0% of patients treated with darolutamide and in 13.4% of patients treated with placebo. The episodes were predominantly of grade 1 or 2 intensity, not associated with any clinically relevant signs or symptoms, and reversible after darolutamide was discontinued. ALT increased of grade 3 and 4 was

reported in 0.9% of patients treated with darolutamide and in 0.3% of patients treated with placebo. AST increased of grade 3 and 4 was reported in 1.2% of patients treated with darolutamide and in 0.3% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased ALT was 253 days and for increased AST 257 days. The mean duration of the first episode was 122 days for ALT increase and 121 days for AST increase. Two and 3 patients were discontinued from treatment due to increase in ALT and AST, respectively.

Fatigue/asthenic conditions

Fatigue

In ARANOTE and ARAMIS pool, fatigue/asthenic conditions were reported in 13.7% of patients treated with darolutamide and in 11.7% of patients treated with placebo. Events with worst grade of 3 were reported in 0.4% of patients treated with darolutamide and in 0.9% of patients treated with placebo. Fatigue (not including asthenia, lethargy or malaise) occurred in the majority of patients (10.0% of patients treated with darolutamide and 8.5% of patients treated with placebo).

Ischaemic heart disease and heart failure

Ischaemic heart disease occurred in 3.4% of patients treated with darolutamide and in 2.2% of patients treated with placebo. Grade 5 events occurred in 0.4% of patients treated with darolutamide and 0.4% of patients treated with placebo. Heart failure occurred in 1.6% of patients treated with darolutamide and in 0.9% of patients treated with placebo.

Bone fractures (excluding pathological fractures)

TEAEs of bone fractures occurred with balanced incidences in the darolutamide and placebo arms (4.1% [EAIR per 100 PY: 2.7] and 3.2% [EAIR: 2.7], respectively).

Fall

In ARANOTE study and the pool safety database, the incidence of fall events was balanced between darolutamide and placebo arms (0.8 per 100 PY vs 0.6, and 2.1 per 100 PY vs 3). Most participants with TEAEs of fall had Grade 1 or 2 events.

Diabetes mellitus and hyperglycemia

In ARANOTE, no notable difference is observed between the treatment arms in the incidence of diabetes mellitus and hyperglycemia AEs (9.0% [EAIR per 100 PY: 5.3] and 9.5% [EAIR: 6.7], respectively), and these events were grade 1 or 2 in most participants. No such event in either treatment arm led to permanent drug discontinuation.

Breast disorders/gynecomastia

In ARANOTE study, breast disorder/gynecomastia events occurred with higher incidence in the darolutamide compared to placebo arms (1.3% [EAIR per 100 PY: 0.8] and 0.9% [EAIR: 0.6], respectively). No event was serious. No event led to study drug permanent discontinuation, interruption, or reduction. Nevertheless, in the safety pool, TEAEs of breast disorder/gynecomastia occurred with balanced incidence in the darolutamide and placebo arms (2.0% [EAIR per 100 PY: 1.3] and 1.4% [EAIR: 1.2], respectively). Gynecomastia was the most frequently reported PT in both treatment arms and at comparable incidences (darolutamide: 1.6% vs placebo: 1.0%).

Vasodilatation and flushing

In ARANOTE study, the incidence of vasodilatation and flushing TEAEs was higher in the darolutamide arm, (9.2% vs 7.2%) but the EAIRs per 100 PY were slightly higher (5.6 vs 5.0). All events were Grade 1 or 2 in both treatment arms. No event was serious or led to permanent study drug discontinuation or

reduction. Considering low relevance of flushing events as shown by absence of permanent treatment discontinuations and low incidence of treatment interruptions, in the darolutamide arm, the observed slight difference between both arms is not considered clinically meaningful.

Rash

Rash is an ADR of darolutamide. In the safety pool, rash TEAEs occurred with higher incidence in the darolutamide arm compared to placebo (3.4% [EAIR per 100 PY: 2.2] and 1.7% [EAIR: 1.4], respectively). Most participants who experienced rash had Grade 1 (darolutamide: 1.1% vs placebo: 0.9%) or Grade 2 events (darolutamide: 0.6% vs placebo: 0.3%). The incidence of Grade 3 events of rash was low and balanced between the treatment arms (darolutamide: 0.3% vs placebo: 0%). No Grade 4 or Grade 5 event was reported.

Hypertension

In ARANOTE study, hypertension events occurred in 9.4% of patients in the darolutamide arm and in 9.5% of patients in the placebo arm. The incidence was similar between darolutamide and placebo arms (5.5 vs. 6.7 per 100 PY, respectively) after adjusting for the duration of treatment. Most participants with such events had grade 2 or grade 3 events (darolutamide vs placebo): grade 1 (1.3% vs 0.9%), grade 2 (3.4% vs 4.5%), and grade 3 (4.7% vs 4.1%). No grade 4 or grade 5 events were reported.

In the safety pool, TEAEs of hypertension occurred with comparable incidences in the darolutamide and placebo arms (8.0% [EAIR per 100 PY: 5.4] and 7.0% [EAIR: 6.0], respectively).

Mental impairment disorders

In the safety pool, TEAEs of mental impairment disorders occurred with balanced incidences in the darolutamide and placebo arms (1.6% [EAIR per 100 PY: 1.1] and 1.4% [EAIR: 1.2], respectively).

Depressed mood disorders

There is no evidence to indicate an increased risk of depressed mood disorders for participants when darolutamide treatment is added to ADT.

Interstitial lung disease

In ARANOTE study, TEAEs of interstitial lung disease occurred with lower incidence in the darolutamide arm (0.2% [EAIR per 100 PY: 0.1]) compared to placebo arm (0.5% [EAIR: 0.3]).

In the safety pool, TEAEs of interstitial lung disease occurred with higher incidences in the darolutamide compared to placebo arm (0.5% [EAIR per 100 PY: 0.3] and 0.1% [EAIR: 0.1], respectively). Neither event was serious. Neither event affected treatment dosing. Neither event was considered related to the treatment by the investigator. Pneumonitis and interstitial lung disease should continue to be closely monitored.

Additional primary malignancies

In ARANOTE study, additional primary malignancies were reported with higher incidence in darolutamide arm (2.7% [EAIR per 100 PY: 1.5] compared to placebo: 0.9% [EAIR: 0.6]). No particular neoplasm or cluster of neoplasms is identified as having an increased incidence in the darolutamide arm. Notably, in the darolutamide arm, half of the participants (6/12) who experienced additional primary malignancies, also reported prior or concomitant radiotherapy. No case was considered related to darolutamide by the investigator. In the safety pool, additional primary malignancies AEs occurred with balanced incidences between the darolutamide and placebo arms (2.8% [EAIR per 100 PY: 1.8] and 2.2% [EAIR: 1.8], respectively). Within the pool, there were 2 participants with grade 4 events (diffuse large B-cell lymphoma in 1 participant and lymphoma in another participant) and 1 additional participant with a

Grade 5 event (pancreatic carcinoma) in the darolutamide arm. Carcinogenicity potential is identified as an important potential risk in the RMP.

Cerebral ischemia/cerebral and intracranial hemorrhage

In ARANOTE study, TEAEs of cerebral ischemia (0.2% vs. 1.4%) and cerebral and intracranial hemorrhage (0.4% vs. 0.5%) did not occur at a higher incidence in darolutamide arm. One cerebrovascular accident event led to treatment interruption and was assessed as related to darolutamide by the investigator.

In the safety analysis pool, TEAEs of cerebral ischemia (1.0% vs 1.4%) and cerebral and intracranial hemorrhage (0.3% vs 0.4%) did not occur at a higher incidence in darolutamide arm.

Based on the clinical data available, no evidence was found for an increased risk of cerebrovascular disorders when darolutamide treatment is added to ADT.

Cardiac disorders

The overall incidence of TEAEs in the SOC cardiac disorders was higher in the darolutamide arm compared to placebo arm (12.4% [EAIR per 100 PY: 7.3) vs 9.0% [EAIR: 6.3]). The higher incidence of cardiac disorders in the darolutamide arm was primarily due to cardiac arrhythmias (8.8% vs 6.8% (EAIR per 100 PY: 5.1 vs 4.7)) and coronary artery disease (3.6% vs 1.4% (EAIR per 100 PY: 2.0 vs 0.9)) rather than heart failure (0.9% vs 0.9% (EAIR per 100 PY: 0.5 vs 0.6)).

2.5.2. Conclusions on clinical safety

Overall, the safety profile of darolutamide is considered manageable. No new safety concerns were identified in this extension of indication for darolutamide in combination with ADT for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC).

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 an updated RMP version with this application (RMP version 5.1).

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

Safety concerns

Table 51 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

No new pharmacovigilance activities

Risk minimisation measures

Table 52: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

• Safety concern	• Risk minimisation measures	• Pharmacovigilance activities
	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
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 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.

• Safety concern	• Risk minimisation measures	• Pharmacovigilance activities
	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	

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, 4.8 and 5.1 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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The purpose of the current submission is to extend the indication for darolutamide to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.

The recommended indication is:

NUBEQA is indicated for the treatment of adult men with:

- metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (see section 5.1).

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.

ADT is recognized as a standard of care for the treatment of mHSPC (NCCN 2025, ESMO 2023). Nevertheless, ADT in monotherapy is discouraged unless there are clear contraindications to combination therapy (NCCN 2025). Moreover, ADT alone should be used only in vulnerable men who cannot tolerate treatment intensification according to ESMO Clinical Practice Guideline considering treatment intensification and use of novel systemic agents (ESMO 2023).

Indeed, ADT with treatment intensification could be also the treatment optimisation and is strongly recommended for patients with mHSPC. Treatment intensification options include doublet therapy of ADT with abiraterone, apalutamide, or enzalutamide (all category 1); triplet therapy of ADT with docetaxel and abiraterone or darolutamide (categories 1) (NCCN2025).

From ARASENS results, combining ADT with docetaxel and darolutamide in men with mHSPC improved OS versus ADT–docetaxel (HR 0.68, 95% CI 0.57-0.80, P < 0.0001). These recommendations highlighted also that combining ADT with docetaxel–abiraterone–prednisone in men with de novo mHSPC improved both rPFS (HR 0.50, 99.9% CI 0.34-0.71, P < 0.0001) and OS (HR 0.75, 95.1% CI 0.59-0.95, P = 0.017) versus ADT–docetaxel (PEACE study). ESMO specifies that in men with mHSPC, ADT alone should be used only in vulnerable men who cannot tolerate treatment intensification.

Recent publications have shown that multiple determinants are associated with lack of treatment intensification, e.g. patient- and disease-related characteristics such as older age, comorbidities, and performance status (Dodkins et al. 2024, Raval et al. 2024). For this patient's population the ADT in monotherapy is still considered a valid option.

3.1.3. Main clinical studies

Efficacy data in support of this application focus on data from trial ARANOTE (study 21140): a Phase III, multinational, randomized (2:1), double-blind, placebo-controlled study evaluating darolutamide in addition to ADT (LHRH agonist/antagonists or orchiectomy) vs. placebo in addition to ADT in the treatment of patients with mHSPC.
Patients were randomized in a 2:1 ratio to receive one of the following study drugs:

- Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg
- Placebo darolutamide matched tablets in appearance, twice daily with food.

Eligible patients must have started ADT (LHRH agonist/antagonist or orchiectomy) no longer than 12 weeks before randomization; had an ECOG PS of 0, 1, or 2; and adequate bone marrow, liver, and renal function.

3.2. Favourable effects

Darolutamide met its primary endpoint and demonstrated a statistically significant improvement and consistent benefit in rPFS compared to placebo in participants with mHSPC across multiple timepoints. The HR was 0.541 (95% CI: [0.413; 0.707]; one-sided p<0.0001), representing a 45.9% reduction in the risk of radiological progression or death in the darolutamide arm compared to the placebo arm. A consistent rPFS benefit for darolutamide was observed across all prespecified sensitivity analyses and all prespecified subgroups, including race, geographic region, presence of visceral metastases, prior local therapy and high and low volume subgroups.

Since OS was not statistically significant at the prespecified alpha significance level of 0.0185 (one-sided) based on 163 OS events observed, the other secondary endpoints were not formally tested for statistical significance according to the hierarchical gatekeeping procedure and results have to be interpreted with caution. Nevertheless, a benefit in favour of darolutamide seems to be observed for all other secondary endpoints compared with placebo.

A final OS analysis with a database new cut-off date (10 JAN 2025) has been provided by the MAH. At the new cut-off date, 185 OS events have occurred: 115 participants in the darolutamide arm and 70 participants in the placebo arm. The median follow-up time for OS was 31.4 months for the darolutamide arm and 30.5 months for the placebo arm. A positive trend in favor of darolutamide was observed for the key secondary endpoint, OS, with an HR of 0.776 (95% CI: [0.577; 1.045]; one-sided p=0.0473). The subgroup analyses of OS showed also a trend in favor of darolutamide in all prespecified subgroups.

3.3. Uncertainties and limitations about favourable effects

While the interim analysis of the key secondary endpoint (OS) did not demonstrate a statistically significant improvement of OS in favour of darolutamide over placebo, with the submission of the final OS analysis, a positive trend in favor of darolutamide was observed which is important to conclude on the clinical benefit of Darolutamide in ARANOTE trial.

Patients with mHSPC eligible to chemotherapy were not excluded in ARANOTE study (eligibility criteria), their proportion and their distribution in both arms are unknown and it is not possible to isolate the effect of darolutamide in this subgroup.

The comparator arm in the ARANOTE study is considered suboptimal as ADT alone is no longer considered as SoC in patients with mHSPC front of the availability of therapies approved in combination with ADT, with notably clinical survival benefit.

3.4. Unfavourable effects

The safety data of darolutamide in the proposed indication (mHSPC) are mainly based on the ARANOTE study, including 445 patients in the darolutamide arm and 223 patients in the placebo arm concurrently with ADT.

Supportive safety data are derived from pooled analysis of ARANOTE and ARAMIS studies (N=2174).

In the pivotal study, the overall time under treatment was longer in the darolutamide arm than in the placebo arm (18.2 vs 11.6 months, respectively). The TEAEs that remained higher in the darolutamide arm than the placebo after adjusting for the treatment duration were blood bilirubin increased (2.4 vs 0.6), AST increased (5.7 vs 5.3).

TEAEs with a worst grade of 3 or 4 reported with a higher incidence in the darolutamide arm than in the placebo arm were ALT increased (2% vs 0.5%), AST increased (2.2% vs 0.5%), and hypertension (4.3% vs 3.6%).

TESAEs were reported with balanced incidences between the darolutamide and placebo arms (23.6% and 23.5%, respectively). Few TESAEs were experienced by ≥1% of participants in either treatment arm.

TEAEs resulting in death (grade 5) occurred in 4.7% and 5.4% of patients in the darolutamide and placebo arms, respectively.

Increased AST, increased ALT, rash, neutrophil count decreased and blood bilirubin increased are ADRs of darolutamide.

3.5. Uncertainties and limitations about unfavourable effects

N/A.

3.6. Effects Table

Table 53: Effects Table for [darolutamide in mHSPC in combination with androgen deprivation therapy] (Primary completion database cut-off date: 07 JUN 2024)

Effect	Short description	Unit	Darolutamide + ADT N=446	Placebo + ADT N=223	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint						
rPFS	Radiological progression-free survival	Median (months) [95% CI] (months)	A [A, A]	25.0 [19.0, A]	HR 0.541 [0.413, 0.707] p<0.0001	ARANOTE Study
Secondary endpoint						
OS*	Overall survival	Median (months) [95% CI] (months)	A [A, A]	A [A, A]	HR 0.776 [0.577, 1.045] P=0.0473	ARANOTE Study
Unfavourable Effects						
Grade ⩾3 TEAEs		Rate (%)	35.5	35.7		ARANOTE Study CSR
SAEs		Rate (%)	23.6	23.5		ARANOTE Study CSR
AEs leading to treatment discontinuation		Rate (%)	6.1	9		ARANOTE Study CSR
Deaths**	Due to TEAEs	Rate (%)	4.7	5.4	One event of death considered related to treatment.	ARANOTE Study CSR
Fatigue/asthenia		Rate (%)	5.6	8.1		ARANOTE Study CSR
AST increased		Rate (%)	9.7	7.7		ARANOTE Study CSR
Blood bilirubin increased		Rate (%)	4.3	0.9		ARANOTE Study CSR
ALT increased		Rate (%)	9.0	8.1		ARANOTE Study CSR

Abbreviations: A=Value cannot be estimated due to censored data; ADT=Androgen deprivation therapy;CI=Confidence interval; OS=Overall survival; rPFS=Radiological progression-free survival

(*) OS was not statistically significant at the prespecified alpha significance level of 0.0202 (one-sided) based on final OS data cut-off date 10 JAN 2025.

(**) male with disease Stage IV B and Gleason score of 8; primary cause of death unknown.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The final rPFS analysis of study ARANOTE showed statistically and clinically meaningful improvements with darolutamide plus ADT treatment compared to placebo plus ADT in men with mHSPC. The benefit of darolutamide on rPFS was consistent and supported by subgroups and sensitivity analyses. These rPFS results are in line with previously approved products of the same class and in the same setting.

Although the interim analysis of the key secondary endpoint (OS) did not demonstrate a statistically significant improvement in favour of darolutamide over placebo, the final OS analysis, provided during the assessment, showed a positive trend in survival in favour of darolutamide.

ADT alone is not the preferred option in patients potentially eligible to chemotherapy. However, the proportion of patient eligible to chemotherapy and their distribution in both arms are unknown and it is not possible to isolate the effect of darolutamide in this subgroup. The CHMP accepts the justification provided to support the administration of darolutamide in patients potentially eligible to chemotherapy, although the study could have been amended with the evolution of SOC (see section 2.4.3. Discussion on clinical efficacy).

The safety profile of darolutamide can be considered manageable. Elevation of ALT was considered an ADR associated with darolutamide. The description of liver function test special event was previously updated to include information on liver function test abnormalities suggestive of idiosyncratic drug-induced liver injury.

3.7.2. Balance of benefits and risks

Study ARANOTE showed a statistically significant and clinically relevant treatment effect on radiological progression free survival of darolutamide + ADT compared to ADT alone in patients with mHSPC.

Study ARANOTE showed a positive trend in favour of darolutamide for the key secondary endpoint OS excluding a detrimental effect.

New safety data in the target indication are overall consistent with the known safety profile of darolutamide, and manageable with adequate risk minimisation measures.

3.7.3. Additional considerations on the benefit-risk balance

N/A.

3.8. Conclusions

The overall B/R of darolutamide in combination with androgen deprivation therapy for the treatment of adult men with mHSPC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 19 out of 31 votes, 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 for NUBEQA to include the treatment of adult men with metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy (ADT) (mHSPC), based on final results from study 21140 (ARANOTE); this is a randomized, double-blind, placebo-controlled Phase 3 study of darolutamide to demonstrate the superiority of darolutamide in addition to ADT over placebo plus ADT in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and update the Package Leaflet to more patient friendly wording based on patient council feedback.

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

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.

Divergent positions to the majority recommendation are appended to this report.

Appendix

1. Divergent positions dated 19 June 2025

DIVERGENT POSITION DATED 19 June 2025

Nubeqa (darolutamide) EMEA/H/C/004790/II/0024

The CHMP expressed a positive opinion to extend the indications of Nubeqa (darolutamide) to the treatment of adult men, with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

This extension of indication is mainly based on the data derived from study ARANOTE, a multicenter, randomized, double-blind, placebo-controlled, phase 3 study designed to determine if darolutamide in addition to ADT (LHRH agonist/antagonists or orchiectomy) is superior to placebo plus ADT by improving radiological progression-free survival (rPFS) in participants with mHSPC.

The undersigned member(s) of the CHMP do not agree that a positive Benefit/Risk has been demonstrated.

Although the study showed a statistically significant treatment effect on rPFS of darolutamide + ADT over ADT alone in ARANOTE, major uncertainties remain. This concerns the comparator arm that is considered sub-standard. ADT alone is no longer considered an acceptable standard of care in EU in the heterogeneous all-comer population of patients with mHSPC and was not considered acceptable before the start of the study in 2020. Docetaxel with or without darolutamide, abiraterone acetate with prednisolone, enzalutamide, and apalutamide are approved in combination with ADT, and associated with statistically significant clinical survival benefit and are advocated by current treatment guidelines.

In addition, the final analysis of Overall Survival did not demonstrate a statistically significant improvement in OS in favour of darolutamide over placebo.

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