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Official Title:	Open-label study of **A**ndrogen **R**eceptor Inhibition with d**A**rolutamide plus Androgen Deprivation Therapy (ADT) Versus ADT in men with Metastatic Hormone-**S**ensitive Prostate Cancer Using an **E**xternal **C**ontrol Arm (ARASEC)
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Title Page

Protocol Title:

Open-label study of **A**ndrogen **R**eceptor Inhibition with d**A**rolutamide plus Androgen Deprivation Therapy (ADT) Versus ADT in men with Metastatic Hormone-**S**ensitive Prostate Cancer Using an **E**xternal **C**ontrol Arm (**ARASEC)**

Protocol Number: 21516

Protocol Version: 6.0

Compound: BAY 1841788 / darolutamide / ODM–201

Study Phase: Phase 2

Short Title:

Open-label external control arm study of darolutamide plus ADT in men with mHSPC

Acronym: ARASEC

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifier Number(s)

IND: 114769

Approval Date: 02 MAY 2025

Protocol Amendment Summary of Changes Table

This amendment is a global amendment dated 02 MAY 2025.

Overall Rationale for the Amendment:

An extension phase of the ARASEC study is added to include an additional year of survival follow-up with mandatory safety collection.

This additional year of follow-up will provide more overall survival related data, to better assess the descriptive survival outcomes outlined in the updated statistical considerations section.

Following final study completion, defined as one-year post-primary completion, study drug will be discontinued, and patients can transition to an available standard of care at the discretion of the investigator (Figure 1-2).

Section # and Name	Description of Change	Brief Rationale
1. Treatment group and duration 1.2 1.3 (SoA) 4.1 4.4 6.7 7. 9.4	The option for participants currently receiving treatment in this study to continue treatment in an extension phase was added. Overall design sections are amended to describe the primary completion and post primary completion in the extension phase. The end of the study was defined.	This additional year follow-up will provide more survival events, to better assess the descriptive survival outcomes. To enable participants who are receiving darolutamide treatment in the current study to continue to receive darolutamide treatment when the study reaches the primary completion.
1. Table 1 1	Old text To assess the frequency of adverse events and the safety of darolutamide combined with ADT versus ADT alone New text To assess the frequency of adverse events and the safety of darolutamide combined with ADT.	ECOG-ACRIN cancer research group provided CHAARTED study adverse events (AEs) data for the treated arm alone.
1. Overall design §3	Old text Matching will be performed using baseline characteristics (age, ECOG PS, extent of disease defined as low volume versus high volume, presence of bone and visceral metastases) in the CHAARTED trial. New text Matching was to be performed using baseline characteristics (age, ECOG PS, extent of disease defined as low volume versus high volume,	Recommendations from the study steering committee

Section # and Name	Description of Change	Brief Rationale
	presence of bone and visceral metastases) in the CHAARTED trial. On recommendations from the study steering committee, the actual matching, conducted shortly after the last ARASEC participant was enrolled, additionally used prior local therapy, Gleason score and baseline PSA.	
2.3 §3	Updated text Cases of idiosyncratic drug-induced liver injury (DILI) with increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to ≥5 and ≥20 x upper limit of normal (ULN), including with concomitant bilirubin elevation >2x ULN, have been reported with darolutamide. Liver function test (LFT) abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug, should discontinue study drug.	Update of the language to remove the time to onset in months for DILI and to clarify the discontinuation criteria with DILI to study drug relatedness.
5.1 (item 11)	New text During the treatment period and for at least 1 week after the last dose of study treatment, sexually active male participants must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol, and refrain from donating sperm during the Treatment period and for at least 1 week after the last dose of study treatment.	Updated wording to align with appendix 4 (Section 10.4).
6.6 7.1 10.3.5	New text Participants who experience hepatic transaminase elevations suggestive of idiosyncratic drug induced liver injury (DILI) considered to be causally related to study drug should discontinue study drug. Please see Section 7.1	Rewording of DILI language to clarify the relationship with the treatment for discontinuation criteria of study drug and harmonization throughout.

Sponsor Signatory

This document is electronically signed. The eSignature is archived in the trial master file (TMF) and can be provided upon request.

PPD PPD, Nubeqa	**Date**

Medical Monitor Name and Contact Information will be provided separately

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List of abbreviations [and Definitions of terms]

ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ARI	Androgen receptor inhibitor
AST	Aspartate aminotransferase
BBB	Blood-brain barrier
BCRP	Breast cancer resistance protein
BHA	Bone health agents
bid	Twice a day
BP	Blood pressure
BUN	Blood urea nitrogen
CAB	Complete androgen blockade
CI	Confidence interval
CIOMS	Council for international organizations of medical sciences
C_{max}	Maximum concentration
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
PFS	Progression-free survival
CrCL	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DB	Double blind
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DTP	Darolutamide treated population
EAU	European association of urology
ECG	Electrocardiogram
ECOG PS	Eastern cooperative oncology group performance status
eCRF	Electronic case report form
EMA	European medicines agency
EOT	End of treatment
EP	Endpoint
FAS	Full analysis set
FDA	US Food and drug administration
GCP	Good clinical practice
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
hAR	Human androgen receptor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HDPE	High density polyethylene
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HR	Heart rate
HSPC	Hormone-sensitive prostate cancer
IB	Investigator's brochure
IC	Informed consent
ICF	Informed consent form
ICH (GCP)	International council for harmonization of technical requirements for pharmaceuticals for human use (good clinical practice)
ID	Identification number
IEC	Independent ethics committee
IMP	Investigational medicinal product
INN	International non-proprietary name
INR	International normalized ratio
IRB	Independent review board
ITF	Investigator trial file
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
KM	Kaplan-Meier
LFT	Liver function test
LHRH	Luteinizing hormone releasing hormone
MCH	Mean corpuscular hemoglobin
mCRPC	Metastatic castration-resistant prostate cancer
MCV	Mean corpuscular volume
M-FAS	Match full analysis set
ME-FAS	Match eligible full analysis set
MedDRA	Medical dictionary for regulatory activities
MFS	Metastasis-free survival
mHSPC	Metastatic hormone-sensitive prostate cancer
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NCI	National cancer institute
NCCN	National comprehensive cancer network
NIMP	Non-investigational medicinal product
nmCRPC	Non-metastatic castration-resistant prostate cancer
OS	Overall survival
p.o.	Per os
PC	Prostate cancer
PCWG3	Prostate cancer working group 3
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal investigator
PP	Polypropylene
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
OS	Overall survival

QTc	Corrected QT
QTcF	Corrected QT (Fridericia's formulae)
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
^{99m}Tc	Technetium 99m radionuclide
TEAE	Treatment-emergent adverse event
TMF	Trial master file
ULN	Upper limit of normal
USA/US	United States of America
USPI	US package insert
WBC	White blood cell
WOCBP	Women of childbearing potential

1. Protocol Summary

1.1 Synopsis

Protocol Title: Open-label study of **A**ndrogen **R**eceptor Inhibition with d**A**rolutamide plus Androgen Deprivation Therapy (ADT) Versus ADT in men with Metastatic Hormone-**S**ensitive Prostate Cancer Using an **E**xternal **C**ontrol Arm (**ARASEC)**

Short Title: Open-label external control arm study of darolutamide plus ADT in men with mHSPC.

Rationale:

The overall treatment paradigm of Metastatic hormone-sensitive prostate cancer (mHSPC) has changed in recent years. Indeed, approximately 70-75% of men with mHSPC receive intensification therapy in addition to androgen deprivation therapy (ADT) in the USA. NCCN guidelines recommend ADT with either of the following regimens: apalutamide (cat 1), abiraterone (cat 1), docetaxel (cat 1) or enzalutamide (cat 1). The same recommendation exists in the EAU guidelines.

The majority of mHSPC patients will benefit from ADT + drugs that inhibit the androgen axis, such as inhibitors of CYP17 or androgen receptor inhibitors or ADT + docetaxel combination, as recommended by guidelines. The combination of an androgen receptor pathway inhibitor + ADT with docetaxel was evaluated in ARASENS where participants were randomized to double-blind treatment with either darolutamide or placebo, in combination with ADT with docetaxel. The darolutamide group had a significant reduction in the risk of death by 32.5% (hazard ratio, 0.68; 95% CI, 0.57 to 0.80; $P< 0.0001$) compared with the placebo group. The addition of darolutamide led to improvement in key secondary end points, and the frequency of adverse events was similar in the two groups (Smith *et al.* 2022).

Independently, many men prefer not to receive chemotherapy or are not able to receive chemotherapy, therefore, optimizing the quality of life is of high importance to patients and caregivers. Drug induced adverse events may lead to a reduced quality of life, therefore, drugs with a favorable safety profile could become an optimal treatment option. Docetaxel and abiraterone have shown to have an inferior safety profile compared to androgen receptor inhibitors (Chen *et al.* 2020). Darolutamide has shown to have a favorable safety profile compared to enzalutamide and apalutamide for the treatment of men with nmCRPC (Di Nunno *et al.* 2019, Liu *et al.* 2020). Darolutamide also presents advantages for the treatment of the elderly, who almost invariably have comedications, due to a lesser risk of drug to drug interactions compared to other androgen receptor inhibitors. There is still a high medical need for a combination ADT + darolutamide, which holds the promise of providing efficacy with a favorable safety profile compared to existing treatment options and provides therapy for men who currently are not eligible for any of the available treatments.

The efficacy of darolutamide has been reported in participants with nmCRPC in the ARAMIS study and with mHSPC in the ARASENS study.

Darolutamide has been well tolerated in a number of clinical studies in mCRPC, nmCRPC and mHSPC. Results from the ARAMIS study led to the FDA, EMA and other regulatory authorities' approval of darolutamide for the treatment of men with nmCRPC and results from

the ARASENS study led to FDA approval in patients with mHSPC in combinations with Docetaxel.

Darolutamide has a unique structure with high binding affinity to the Androgen Receptor (AR). It has a favorable Drug - Drug Interaction (DDI) profile, proven efficacy clinical data with a low incidence of adverse events, including those typically associated with the inhibition of the androgen receptor in men with nmCRPC.

Such evidence is providing a strong rationale to conduct a study of darolutamide in men with mHSPC. Due to the changes in the treatment landscape, ADT alone would not be an acceptable comparator in the USA. Consequently, this open label trial in which a contemporary cohort of men with mHSPC will be enrolled and will receive treatment with ADT plus darolutamide will be conducted. The participants enrolled in this arm will be matched with participants from the control arm of CHAARTED, a randomized, controlled trial comparing the efficacy of docetaxel plus ADT combination to ADT alone. The CHAARTED study was previously conducted in the USA (Sweeney *et al.* 2015).

Objectives and Endpoints:

Table 1-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess if the addition of darolutamide to ADT compared with ADT alone would result in superior clinical efficacy in participants with metastatic hormone-sensitive prostate cancer (mHSPC) by superior progression-free survival (PFS)	• PFS (PFS defined as the time interval from enrollment [a] to PSA progression [b], clinical progression or death, whichever occurs first. Clinical progression is defined as increasing symptomatic bone metastases, radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases, or clinical deterioration due to cancer per investigator's opinion)
Secondary	
• To assess if the addition of darolutamide to ADT compared to ADT alone can prolong overall survival	• Overall survival (OS) (Defined as time from the date of enrollment until death resulting from any cause or the date last known alive)
• To assess radiographic progression-free survival in participants who received darolutamide plus ADT	• Radiographic Progression-free survival (rPFS) (Defined as time from enrollment to investigator-assessed radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases or death, whichever occurs first)
• To assess if the addition of darolutamide to ADT compared to ADT alone can increase the time to castration-resistant prostate cancer (CRPC)	• Time to castration-resistant prostate cancer (CRPC) (Defined as the time from enrollment until documented clinical or PSA progression with a testosterone level of less than 50 ng per deciliter or documented medical castration or surgical castration])
• To assess the complete PSA response rate at 6 months in the ADT + darolutamide arm vs ADT alone	• Complete PSA response rate at 6 months from enrollment date [a] (Defined as a PSA level of less than 0.2 ng per milliliter on two consecutive measurements at least 4 weeks apart)
• To assess the frequency of adverse events and the safety of darolutamide combined with ADT	• Adverse Events will be assessed by NCI CTCAE (v. 5.0)

Abbreviations: ADT = androgen deprivation therapy; PFS = progression-free survival; mHSPC = metastatic hormone-sensitive prostate cancer; RECIST = Response Evaluation Criteria In Solid Tumors (v. 1.1); CRPC = castration-resistant prostate cancer; PSA = prostate specific antigen; OS = overall survival; NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events

a. Enrollment for the active arm of this study is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria. This date may be used for matching with the control arm and is considered equivalent to randomization date from the CHAARTED study, thus, enrollment for the control arm is defined as the date of randomization of participants in the CHAARTED study.

b. See definition in Section 3.

Overall Design:

This is a phase 2 open label study using an external control arm, to assess if the addition of darolutamide to ADT provides superior efficacy in terms of progression-free survival (PFS), as compared to ADT alone in men diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC).

The primary endpoint is progression-free survival (PFS). This is the time interval from enrollment to PSA progression, clinical progression or death, whichever occurs first. Clinical progression is defined as increasing symptomatic progression in bone, radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases, or clinical deterioration due to cancer per investigator's opinion/assessment.

Approximately 200 mHSPC participants will receive darolutamide plus ADT in the ARASEC active treatment arm within 3 days since enrollment.* Additional participants may be enrolled in the event of a lower matching rate. The control arm for the study will be derived from the 394 participants treated with ADT alone in the CHAARTED trial. Active arm participants will be matched to control arm participants in a 1:1 ratio. Matching was to be performed using baseline characteristics (age, ECOG PS, extent of disease defined as low volume versus high volume, presence of bone and visceral metastases) in the CHAARTED trial. On recommendations from the study steering committee, the actual matching, conducted shortly after the last ARASEC participant was enrolled, additionally used prior local therapy, Gleason score and baseline PSA.

*Enrollment for the active arm of this study is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria.

Disclosure Statement: This is an open label, single arm study using an external control arm.

Number of Participants:

Approximately 200 participants are planned to be treated in this study. Additional participants may be enrolled in the event of a lower matching rate.

Treatment Groups and Duration:

All participants will receive darolutamide 600 mg bid plus ADT. The study duration will be from the first participant’s first visit until study completion.

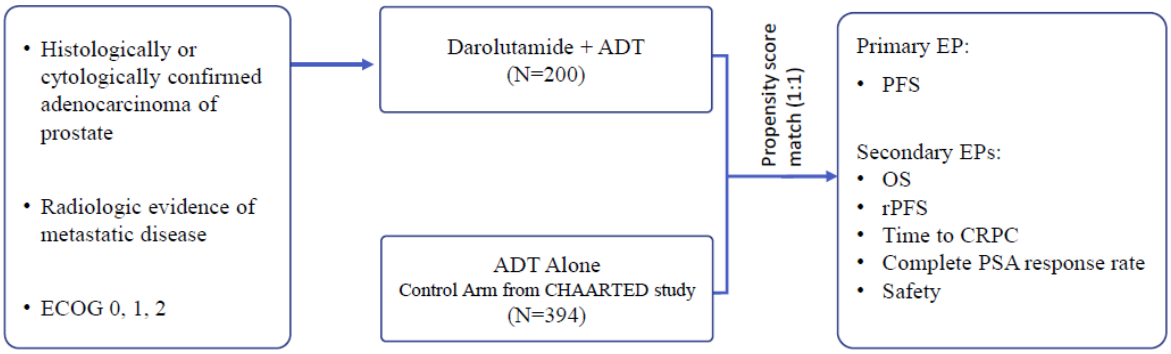
Primary Completion and Study Completion

The primary completion is defined as when either the primary endpoint has been met or all participants have been followed (including Survival Follow-up) for at least 2 years after enrollment, whichever occurs later, unless the participant withdrew, died or was lost to follow-up. Following final study completion, defined as one year post-primary completion, study drug will be discontinued and patients can transition to an available standard of care at the discretion of the investigator.

Data Monitoring Committee: No

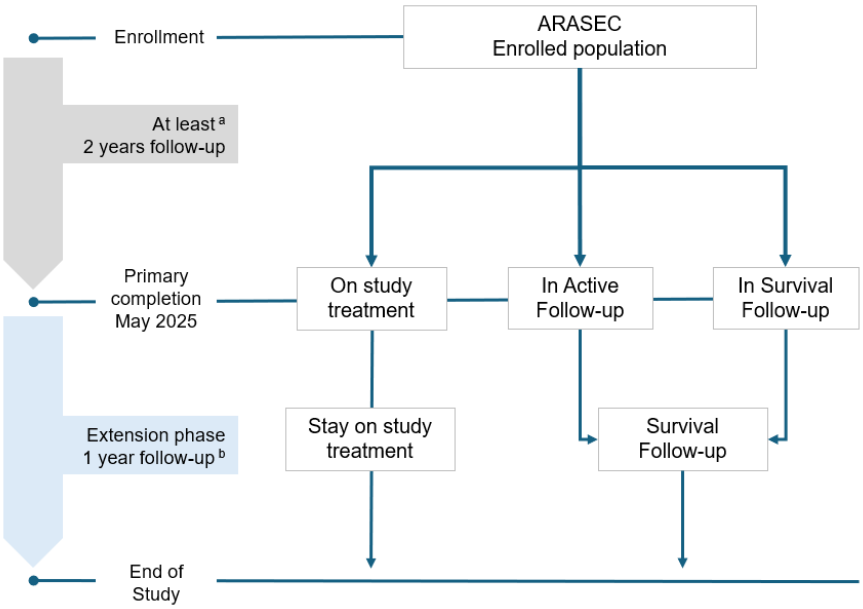
1.2 Schema

Figure 1-1. Study schema



Abbreviations: ADT = androgen deprivation therapy; EP = endpoint; PFS = progression-free survival; CRPC = castration-resistant prostate cancer; PSA = prostate specific antigen; OS = overall survival.

Figure 1-2. Study timeline



a. Either the primary endpoint has been met, or all participants have been followed (including Survival Follow-up) for at least 2 years after enrollment, whichever occurs later, unless the participant withdrew, died or was lost to follow-up.
b. At the time of the primary completion, all participants remaining on the study will be moved into the extension phase. Final study completion will occur after an additional year of participant follow-up following primary completion, with limited data collection to facilitate descriptive analyses of survival.

1.3 Schedule of Activities (SoA)

Table 1-2: Schedule of activities until the primary completion

Procedure	**Screening**		**Treatment Period [Days or Weeks, etc.]**				
	Within 28 days before enrollment [a]	Within 7 days before enrollment	**Week 1 Day 1**	**Subsequent visits** (every 12 weeks, ± 7 days) [b]	**EOT Visit:** 30 days (+7 days) after last dose of darolutamide [c]	**Active Follow–up Visits** [d] (approx. every 12 weeks after EOT visit until PSA or clinical progression)	**Survival Follow-up** [e] (approx. every 12 weeks until Primary completion)
Informed consent	X						
Eligibility criteria	X						
Demography	X						
Medical history	X						
PC history (incl. pre-treatments and procedures)	X						
Physical examination (including skin, weight and height) [f,g]	X			X	X	X	
12–lead ECG [f,h]		X			X		
Echocardiogram/MUGA [i]	X						
Vital signs (BP, HR) [f,g]		X		X	X		
Laboratory safety assessments (hematology, general chemistry, including liver chemistries)	X			X	X		
Laboratory safety assessments (coagulation)	X						
Serum PSA	X			X	X	X	

Table 1-2: Schedule of activities until the primary completion

Procedure	**Screening**		**Treatment Period [Days or Weeks, etc.]**				
	Within 28 days before enrollment [a]	Within 7 days before enrollment	**Week 1 Day 1**	**Subsequent visits** (every 12 weeks, ± 7 days) [b]	**EOT Visit:** 30 days (+7 days) after last dose of darolutamide [c]	**Active Follow–up Visits** [d] (approx. every 12 weeks after EOT visit until PSA or clinical progression)	**Survival Follow-up** [e] (approx. every 12 weeks until Primary completion)
Testosterone	X			X	X	X	
ECOG PS	X			X	X		
CT/MRI [j,k]	See footnote [j]			(X)	(X)	(X)	(X)
Bone scan [j,k]	See footnote [j]			(X)	(X)	(X)	(X)
AEs/SAEs [l]	X	X	X	X	X	X	X
Concomitant treatments [m,]	X	X	X	X	X	X	X[n]
Darolutamide administration[o]			X	X			
Subsequent antineoplastic therapy assessment [p]						X	X
Survival status							X[q]

Note: (X) indicates an optional assessment.

a. Enrollment for the active arm of this study is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria.
b. Date of visit is to be calculated from the previous visit date.
c. The EOT visit will be completed before starting a new antineoplastic therapy, if it starts sooner than 30 days (+7 days) after the last dose of study drug.
d. After EOT, the participants who discontinued darolutamide treatment for reasons other than disease progression will be followed during the Active Follow-up period until documented disease progression.
e. Survival follow-up visit may be performed by remote confirmation.
f. Order of assessments: Ensure that ECG and vital signs are collected prior to blood draw.

g. Vital signs measurements include temperature, systolic and diastolic blood pressure, and heart rate.
h. An ECG is to be performed at subsequent visits if indicated by the investigator.
i. A left ventricular fraction ejection will be assessed at baseline. Follow-up as needed at the discretion of the investigator.
j. Contrast–enhanced chest, abdomen, and pelvic CT or MRI and bone scan will be performed at baseline to demonstrate metastatic disease. If androgen deprivation therapy has not commenced, scans must be obtained within 6 weeks of enrollment (ADT can start on day of enrollment or prior after scans obtained). If androgen deprivation has commenced prior to enrollment, scans must be obtained within 6 weeks prior to the start of androgen deprivation therapy. If all required imaging had not been completed prior to starting androgen deprivation, then any additional scans must be obtained after starting androgen deprivation but prior to enrollment.
k. Tumor assessment imaging (^{99m}Tc-phosphonate bone scan, chest, abdomen and pelvic CT or MRI) is recommended to be performed in accordance with investigator discretion as clinically indicated and may be performed at any time in case of PSA progression, symptomatic progressive disease, start of new antineoplastic therapy, or if recommended as part of standard of care procedure. Note: (X) indicates an optional assessment. Beyond screening assessment, there are no study specific requirements for tumor imaging assessments and all scans should be performed as per local standard of care practice. All tumor assessment imaging, whenever conducted per investigator's discretion, must be assessed for radiographic progression by a radiologist or the investigator, according to RECIST criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases, until radiographic progression or start of new antineoplastic therapy. This applies to participants who enter the Active Follow-up or Survival Follow-up.
l. AE/SAEs, regardless of causality assessment, must be collected through the last dose of study drug and for 30 days following the study drug discontinuation. After 30 days following study drug discontinuation, only any SAE judged by the investigator to be related to the study treatment must be reported up to the end of the study.
m. Including bone health agents (BHA) according to local guidelines for participants with risk of bone fracture.
n. Concomitant medications in patients with related SAEs.
o. Eligible participant (eligibility documented and confirmed) will start darolutamide administration twice daily in addition to ADT within 3 days since enrollment.
p. Use of post-study antineoplastic therapy will also be collected for participants with hormone refractory disease.
q. Participants who are ongoing at the time of primary endpoint data cutoff will be followed up for survival for up to 24 months from study entry of the last participant.

Table 1-3: Extension Phase Schedule of Activities

	Treatment period	**Post treatment/Follow-up**	
	Subsequent visits (every 12 weeks, ± 7 days) [a]	**EOT Visit:** 30 days (+7 days) after last dose of darolutamide [b, c]	**Survival Follow–up** [d] (approx. every 12 weeks until study completion)
Informed consent			
Eligibility criteria			
Demography			
Medical history			
PC history (incl. pre-treatments and procedures)			
Physical examination (including skin, weight and height) [e,f]	X	X	
12–lead ECG [e,g]		X	
Echocardiogram/MUGA [h]			
Vital signs (BP, HR) [e, f]	X	X	
Laboratory safety assessments (hematology, general chemistry, including liver chemistries)	X	X	
Laboratory safety assessments (coagulation)			
Serum PSA			
Testosterone			
ECOG PS			
CT/MRI			
Bone scan			
AEs/SAEs [i]	X	X	X

	Treatment period	Post treatment/Follow-up	
	Subsequent visits (every 12 weeks, ± 7 days) [a]	**EOT Visit:** 30 days (+7 days) after last dose of darolutamide [b, c]	**Survival Follow–up** [d] (approx. every 12 weeks until study completion)
Concomitant treatments [j,]	X	X	X[k]
Darolutamide administration [l]	X		
Subsequent antineoplastic therapy assessment [m]			X
Survival status			X

Note: (X) indicates an optional assessment.

a. Date of visit is to be calculated from the previous visit date.
b. The EOT visit will be completed before starting a new antineoplastic therapy, if it starts sooner than 30 days (+7 days) after the last dose of study drug.
c. After EOT, the participants who discontinued darolutamide treatment for reasons other than death will need to be followed during the extension survival follow-up phase (Off study treatment) until documented death or study completion.
d. Survival follow-up visit may be performed by remote confirmation.
e. Order of assessments: Ensure that ECG and vital signs are collected prior to blood draw.
f. Vital signs measurements include temperature, systolic and diastolic blood pressure, and heart rate.
g. An ECG is to be performed at subsequent visits if indicated by the investigator.
h. A left ventricular fraction ejection will be assessed at baseline. Follow-up as needed at the discretion of the investigator.
i. AE/SAEs, regardless of causality assessment, must be collected through the last dose of study drug and for 30 days following the study drug discontinuation. After 30 days following study drug discontinuation, only any SAE judged by the investigator to be related to the study treatment must be reported up to the end of the study.
j. Including bone health agents (BHA) according to local guidelines for participants with risk of bone fracture.
k. Concomitant medications in patients with related SAEs.
l. Eligible participant (eligibility documented and confirmed) will start darolutamide administration twice daily in addition to ADT within 3 days since enrollment.
m. Use of post-study antineoplastic therapy will be collected including for those participants with castrate resistant prostate cancer disease until the end of study.

2. Introduction

Darolutamide is a next-generation nonsteroidal androgen receptor inhibitor (ARI) for the treatment of prostate cancer, which binds with a high affinity and selectivity to AR with potent and improved antagonism for human androgen receptor (hAR). Overall darolutamide antagonizes AR wild type and mutants AR(F876L), AR(W741L), and AR(T877A) known to mediate resistance to first- and second-generation antiandrogens (Moilanen *et al.* 2015, Sugawara *et al.* 2019).

Darolutamide has showed a very low blood-brain barrier (BBB) penetration in rodents (Zurth *et al.* 2019). First data in humans also suggest that darolutamide has a favorable impact on brain blood flow compared to enzalutamide and that this might be attributable to difference in BBB penetration. Differences in BBB penetration of treatment and therefore, the effect on the central nervous system may reduce the risk of CNS related side effects such as cognitive function or the risk of seizures.

Darolutamide demonstrated significant improvement of metastatic free survival (MFS) and Overall Survival (OS) in participants with non-metastatic castrate resistant prostate cancer (nmCRPC) compared to androgen deprivation therapy (ADT) in the Phase III ARAMIS study (Fizazi *et al.* 2019, NUBEQA® 2019). The primary analysis in ARAMIS showed a median metastasis-free survival (MFS) improvement of 22 months (40.4 months in darolutamide compared with to 18.4 months in placebo arms hazard ratio of 0.41; 95% CI 95% CI 0.34 to 0.50). The final analysis showed a statistically significant benefit in overall survival and all other secondary end points such as time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event.

Safety results of pivotal Phase 3 study ARAMIS in nmCRPC showed that darolutamide treatment was well-tolerated, with a comparable incidence of most common treatment-emergent adverse events (TEAEs) and a similar incidence of permanent discontinuations of treatment between the darolutamide and the placebo arms during the Double Blind (DB) period. Incidences of events of interest (including falls, CNS effects, and hypertension) were not increased with darolutamide compared with placebo when adjusted for treatment exposure. The safety analysis of darolutamide has shown that darolutamide was well tolerated in participants with mCRPC (as seen in phase 1/2 studies).

2.1 Study Rationale

The overall treatment paradigm of mHSPC has changed in recent years. Indeed, approximately 70-75% of men with mHSPC receive intensification therapy in addition to ADT in the USA. NCCN guidelines recommend ADT with either of the following regimens: Apalutamide (cat 1), Abiraterone (cat 1), Docetaxel (cat 1) or enzalutamide (cat 1). The same recommendation exists in the EAU guidelines.

The majority of mHSPC patients will benefit from ADT + drugs that inhibit the androgen axis, such as inhibitors of CYP17 or androgen receptor inhibitors or ADT + docetaxel combination, as recommended by guidelines. It is not known whether further intensification with a 3-drug regimen, such as ADT + docetaxel + androgen receptor inhibition, will lead to improved clinical outcomes. This question is expected to be answered in the ongoing ARASENS study. Independently, many men prefer not to receive chemotherapy or are not able to receive chemotherapy, therefore, optimizing the quality of life is of high importance to patients and caregivers. Drug induced adverse events may lead to a reduced quality of life,

therefore, drugs with a favorable safety profile could become optimal treatment option. Docetaxel and abiraterone have shown to have an inferior safety profile compared to androgen receptor inhibitors (Chen *et al.* 2020). Darolutamide has shown to have a favorable safety profile compared to enzalutamide and apalutamide for the treatment of men with nmCRPC (Di Nunno *et al.* 2019, Liu *et al.* 2020). Darolutamide also presents advantages for the treatment of the elderly, who almost invariably have comedications, due to a lesser risk of drug to drug interactions compared to other androgen receptor inhibitors. There is still a high medical need for a combination ADT + darolutamide, which holds the promise of providing efficacy with a favorable safety profile compared to existing treatment options and provides therapy for men who currently are not eligible for any of the available treatments.

The efficacy of darolutamide has been reported in participants with nmCRPC in the ARAMIS study and with mHSPC in the ARASENS study.

Darolutamide has been well tolerated in a number of clinical studies in mCRPC, nmCRPC and mHSPC. Results from the ARAMIS study led to the FDA, EMA and other regulatory authorities' approval of darolutamide for the treatment of men with nmCRPC, and results from the ARASENS study led to FDA approval in participants with mHSPC in combinations with Docetaxel.

Darolutamide has a unique structure with high binding affinity to the Androgen Receptor (AR). It has a favorable Drug - Drug Interaction (DDI) profile, proven efficacy clinical data with a low incidence of adverse events, including those typically associated with the inhibition of the androgen receptor in men with nmCRPC.

Such evidence is providing a strong rationale to conduct a study of darolutamide in men with mHSPC. Due to the changes in the treatment landscape, ADT alone would not be an acceptable comparator in the USA. Consequently, this open label trial in which a contemporary cohort of men with mHSPC will be enrolled and will receive treatment with ADT plus darolutamide will be conducted. The participants enrolled in this arm will be matched with participants from the control arm of CHAARTED, a randomized, controlled trial comparing the efficacy of docetaxel plus ADT combination to ADT alone. The CHAARTED study was previously conducted in the USA (Sweeney *et al.* 2015).

2.2 Background

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death among men worldwide. Based on GLOBOCAN 2018 estimates, 1,276,106 new cases of prostate cancer were reported worldwide in 2018, with higher prevalence in developed countries (Rawla 2019). In 2019, an estimated 174,650 new diagnoses of prostate cancer are expected in the US, with 31,620 expected deaths (Siegel *et al.* 2019). In the US, the incidence of mHSPC, defined as metastatic disease in patients who have not yet received or are continuing to respond to hormone therapy, has increased by approximately 72% between 2004 and 2013, with age standardized incidence rates having significantly risen from 1.45% to 2.74% annually since 2012, most prominently among men aged ≤ 69-year (Chen *et al.* 2014, Jack *et al.* 2010, Norgaard *et al.* 2010). Based on European country specific registries, approximately 6% to 30% of newly diagnosed prostate cancer are mHSPC and more than 50% of patients in regions such as Indonesia have metastatic disease at diagnosis (Kelly *et al.* 2018, Scher *et al.* 2015, Weiner *et al.* 2019).

Metastatic hormone-sensitive prostate cancer (mHSPC) is the disease stage where patients have metastatic prostate cancer and are responsive to androgen deprivation therapy (ADT),

including patients who develop metastatic recurrence after local treatment (surgery and / or radiotherapy) and patients with *de novo* metastatic disease who did not benefit from prior radical procedures.

Newly diagnosed mHSPC is recognized as an aggressive form of the disease with rapid progression to the metastatic castration-resistant state in virtually all patients (Fizazi *et al.* 2019, Vale *et al.* 2016). Historically, androgen deprivation has been the standard of care for mHSPC (Rydzewska *et al.* 2017). Although almost all men with mHSPC initially experience a response to ADT, most will develop metastatic castration-resistant prostate cancer (mCRPC) within 1 to 3 years of their diagnosis (Fizazi *et al.* 2015, Gravis *et al.* 2013, Sweeney *et al.* 2015). Metastatic castration-resistant prostate cancer has poor prognosis and high lethality.

Androgen deprivation therapy can be accomplished either by surgical orchiectomy (castration) or medical castration (using either a luteinizing hormone releasing hormone [LHRH] agonist or a GnRH antagonist). When LHRH therapy is initiated, a transient rise in luteinizing hormone can cause a surge in serum testosterone, which may stimulate prostate cancer growth. The flare phenomenon can be effectively prevented with the addition of an anti–androgen therapy to ADT, a complete androgen blockade (CAB), which blocks the effect of the increased serum testosterone (Heidenreich *et al.* 2014, Loblaw *et al.* 2007, Mohler *et al.* 2014).

Combined androgen blockade using both an LHRH agonist and an antiandrogen has been extensively studied as upfront therapy in mHSPC (Bernard and Sweeney 2015, Liaw *et al.* 2015, Valenca *et al.* 2015). Several meta–analyses have shown a modest 2% to 5% improvement in 5–year survival with CAB over castration, although with increased toxicity. One of the largest meta–analyses included the individual level data of 8,275 subjects from 27 trials. Although there was an overall trend toward improved 5–year survival with CAB over castration, this did not reach statistical significance (P=0.11) (Prostate Cancer Trialists' Collaborative Group 2000, Samson *et al.* 2002, Schmitt *et al.* 2000). According to NCCN prostate cancer guidelines 2014, CAB provides modest to no benefit over castration alone in metastatic patients. Metastatic hormone-sensitive prostate cancer has a well-documented course, and the treatment landscape has rapidly evolved over the last five years. Several randomized trials have demonstrated significant clinical benefit with the addition of docetaxel, abiraterone plus prednisone, enzalutamide or apalutamide to ADT (Cattrini *et al.* 2019, Hahn *et al.* 2018).

The control arm for this study will be derived from the 394 participants treated with ADT alone in the CHAARTED trial. The identification of a suitable external control arm required that the arm be comparable to the enrolled arm with regards to important prognostic factors represented in the participant population. This assessment required access to participant level data for the control participants or a control series derived from clinical trials with well-characterized eligibility and evaluation criteria. Additionally, comparability of response assessment or progression assessment is required when the endpoints are either response rate or progression-free survival (Simon *et al.* 2015). Control participants selected from historical clinical trials, such as CHAARTED, which measured PFS in its participant population, are expected to serve as a suitable option for an external control in this setting.

The CHAARTED trial has demonstrated a significant overall survival (57.6 months) with docetaxel plus ADT compared to ADT alone (47.2 months) in participants with mHSPC (hazard ratio of 0.72; 95% CI, 0.58-0.89;). However, this benefit was not observed in low burden of disease, (hazard ratio of 1.04; 95% CI, 0.7- 1.55) and there was no observable benefit in participants with prior local therapy and low volume disease (Sweeney *et al.* 2015).

2.3 Benefit/Risk Assessment

Darolutamide has undergone an extensive clinical development program and the data have demonstrated efficacy and effectiveness in the treatment of patients with nmCRPC and mHSPC. Darolutamide treatment was well tolerated demonstrating a favorable benefit risk balance, hence approved for the treatment of patients with nmCRPC and mHSPC in combination with docetaxel.

No dose–limiting toxicities were observed in the phase I dose escalation. The safety profile of darolutamide was based on the results of ARAMIS (nmCRPC), ARASENS (mHSPC) and that in pooled analysis of mCRPC (Phase 1/2 studies). The profile of TEAEs was same despite the difference in participant populations, supporting the favorable safety profile of darolutamide. No evidence was found that darolutamide would add any clinically relevant toxicity when administered with ADT. The safety data from Phase 3 study ARAMIS indicated no clinically relevant difference between darolutamide and placebo in the incidence of adverse events that occurred during the treatment period, including falls, fractures, seizures, cognitive disorders, and hypertension. Quality-of-life outcomes were similar in the two groups. Also, in ARASENS Phase 3 study, the incidences of most of the adverse events of special interest for androgen-receptor pathway inhibitors, including fatigue, falls, fractures, mental impairment, and cardiovascular events were similar. In both Phase 3 studies, ARAMIS trial in non-metastatic, castration-resistant and ARASENS trial in metastatic hormone sensitive prostate cancer, there was no more than a 2 percentage-point difference between the darolutamide and placebo groups with respect to the incidence of most adverse events that are commonly associated with androgen-receptor pathway inhibitors (Smith *et al.* 2022). Importantly, participant quality of life was maintained throughout the duration of treatment. Based on the Phase 1/2 ARADES and Phase 1 ARAFOR studies, no dose–related trends were noted in the AE profile. Early phase studies demonstrated that antitumor activity was seen at all dose levels as evaluated by PSA, CTC counts, and soft and bone lesion imaging. In these 2 studies, participants who were naïve to treatment with chemotherapy or CYP17i have responded best to darolutamide treatment.

Cases of idiosyncratic drug-induced liver injury (DILI) with increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to ≥ 5 and ≥ 20 x upper limit of normal (ULN), including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide. Liver function test (LFT) abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug, should discontinue study drug.

With its potent anti–androgenic profile, there is a strong rationale to study darolutamide in patients with mHSPC to delay disease progression and death. The available safety and efficacy data suggest that participants in this trial are not placed at undue risk.

Overall, the benefit/risk assessment for darolutamide in addition to standard ADT therapy for mHSPC patients is favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of darolutamide may be found in the Investigator's Brochure.

3. Objectives and Endpoints

The purpose of this study is to evaluate the efficacy and safety of darolutamide in combination with Androgen Deprivation Therapy (ADT) versus ADT alone, using a matched control arm from the CHAARTED trial as treatment for men diagnosed with Metastatic Hormone-sensitive Prostate Cancer (mHSPC).

The primary hypothesis of this study is that darolutamide in combination with ADT is superior to ADT alone in terms of progression-free survival (PFS).

Table 3-1. Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess if the addition of darolutamide to ADT compared with ADT alone would result in superior clinical efficacy in participants with metastatic hormone-sensitive prostate cancer (mHSPC) by superior progression-free survival (PFS)	• PFS (PFS defined as the time interval from enrollment [a] to PSA progression [b], clinical progression or death, whichever occurs first. Clinical progression is defined as increasing symptomatic bone metastases, radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases, or clinical deterioration due to cancer per investigator's opinion)
Secondary	
• To assess if the addition of darolutamide to ADT compared to ADT alone can prolong overall survival	• Overall survival (OS) (Defined as time from the date of enrollment until death resulting from any cause or the date last known alive)
• To assess radiographic progression-free survival in participants who received darolutamide plus ADT	• Radiographic Progression-free survival (rPFS) (Defined as time from enrollment to investigator-assessed radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases or death, whichever occurs first)
• To assess if the addition of darolutamide to ADT compared to ADT alone can increase the time to castration-resistant prostate cancer (CRPC)	• Time to castration-resistant prostate cancer (CRPC) (Defined as the time from enrollment until documented clinical or PSA progression with a testosterone level of less than 50 ng per deciliter or documented medical castration or surgical castration])
• To assess the complete PSA response rate at 6 months in the ADT + darolutamide arm vs ADT alone	• Complete PSA response rate at 6 months from enrollment date [a] (Defined as a PSA level of less than 0.2 ng per milliliter on two consecutive measurements at least 4 weeks apart)
• To assess the frequency of adverse events and the safety of darolutamide combined with ADT	• Adverse Events will be assessed by NCI CTCAE (v. 5.0)

Abbreviations: ADT = androgen deprivation therapy; PFS = progression-free survival; mHSPC = metastatic hormone-sensitive prostate cancer; RECIST = Response Evaluation Criteria In Solid Tumors (v. 1.1); CRPC = castration-resistant prostate cancer; PSA = prostate specific

antigen; OS = overall survival; NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events.

a. Enrollment for the active arm of this study is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria. This date may be used for matching with the control arm and is considered equivalent to randomization date from the CHAARTED study, thus, enrollment for the control arm is defined as the date of randomization of participants in the CHAARTED study.
b. PSA progression is defined as when the PSA demonstrates an increase that is more than 50% of nadir, taking as reference the lowest recorded PSA level since starting androgen deprivation therapy (ADT). Two consecutive increases must be documented with each measurement obtained at least two weeks apart. On occasions, there may be an intermediate fluctuant value. This will not restart the evaluation period so long as the intermediate value was not below the previous nadir.

The date of first recorded increase (not defeated by a subsequent drop in PSA level to create a new nadir) will be deemed the date of progression.

If a participant achieves a PSA that is less than 4 ng/ml:

• The confirming increase must reach a value that is more than 4.0 ng/ml (the unconfirmed and additional intermediate increases may be a value that is less than 4.0 ng/ml, but greater than 50% of nadir since starting ADT).
• If the participant's nadir is less than 2 ng/ml, the first time the PSA reaches a value greater than 50% of nadir since starting ADT **and** is at least 2 ng/ml will be the date of first progression. However, this progression must be confirmed by a PSA value that is more than 4.0 ng/ml with no intervening declines below 2 ng/ml.

Progression will be declared if participant has documented to have a testosterone level of less than 50 ng/dL. In cases where a testosterone level has not been obtained and participant has not had an orchiectomy (as detailed in the study calendar), PSA progression will be deemed if participant had a documented rise in PSA on LHRH analogue therapy.

4. Study Design

4.1 Overall Design

This is a phase 2 open label single arm study using an external control arm, to assess if the addition of darolutamide to ADT provides superior efficacy in terms of progression-free survival (PFS), as compared to ADT alone for men diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC).

The primary endpoint is progression-free survival (PFS), as defined in Section 3.

Approximately 200 mHSPC participants will receive darolutamide plus ADT in the ARASEC active treatment arm. Additional participants may be enrolled in the event of a lower matching rate. The control arm for the study will be derived from the participants treated with ADT alone in the CHAARTED trial using a matching approach.

The study will comprise the following consecutive periods: Screening, Treatment period, Active Follow–up period and Survival Follow–up period and Extension phase.

Screening period:

After the participant has signed the informed consent, the screening period will begin from the date of signed Informed Consent. Participant screening must occur within 28 days prior to enrollment, during which all study-related procedures and evaluations will be performed in order to establish participant eligibility. Enrollment will take place in the IWRS, where the participant will receive a unique participant ID.

Eligible participants (eligibility documented and confirmed) will start darolutamide administration twice daily in addition to ADT within 3 days since enrollment.

Treatment period:

Participants will receive darolutamide in addition to ADT. The treatment period is defined as the time from the administration of first dose of darolutamide until clinical progression (as defined in Section 3), unacceptable toxicity, withdrawal of consent, investigator's decision to stop therapy for the participant, participant decision to stop therapy, sponsor's decision to terminate the study, or death. All participants will receive and remain on a stable regimen of ADT (LHRH agonist /GnRH antagonists or surgical castration) at the discretion of the investigator.

End of Treatment Visit:

End of Treatment (EOT) visit will be conducted 30 days (+ 7 days) after the last treatment of darolutamide. During the end of treatment (EOT) visit, procedures to monitor participant's health, to identify potential toxicities, to assess efficacy should be performed (Section 1.3).

If a participant had PSA or clinical progression (as defined in Section 3), these participants will be followed up in the Survival Follow-up period. Participants without progression will be followed up in the Active Follow-up period.

Active Follow–up period (until primary completion):

After EOT, the participants who discontinued darolutamide treatment for reasons other than PSA progression or clinical progression (including radiographic progression or symptomatic

progression as defined in Section 3) will be followed during the Active Follow-up period until PSA progression or clinical progression (as defined in Section 3).

During the Active Follow–up period, the following assessments will be performed as defined in the SoA (Table 1-2):

- Assessment of progression:
  - Serum PSA
  - Testosterone
  - Clinical progression assessments as defined in Section 3
  - Radiographic progression as defined in Section 3
- AEs/SAEs (up to 30 days after last study dose)
- Subsequent antineoplastic therapy.

Survival Follow-up period (until primary completion):

Participants who had PSA progression or clinical progression will enter Survival Follow-up period. Participants who are on darolutamide treatment or are in the Active Follow-up at the time of primary endpoint data cutoff will enter Survival Follow-up period until primary completion. During the Survival Follow–up period until study primary completion, the following assessments will be performed as defined in the SoA (Table 1-2):

Related SAEs with concomitant medications received:

- Subsequent antineoplastic therapy
- Survival status
- In case that a participant did not experience radiographic progression and did not start new antineoplastic treatment, tumor imaging assessment for radiographic progression should continue in the Survival Follow-up, as described in the SoA (Section 1.3).

Extension phase (post-primary completion)

Following the primary completion of the study, an additional year of participant follow-up will be conducted with limited data collection to facilitate descriptive analyses of survival.

All participants remaining on the study at the time of the study primary completion will enter the extension phase of the study. Participants will continue undergoing the following assessment per Table 1-3.

- Patients who remain under treatment:
  - Physical examination
  - Vital signs (BP, HR)
  - Laboratory safety assessments (hematology, general chemistry, including liver chemistries)
  - AEs/SAEs
  - Darolutamide administration
- Patients who are not on study treatment and are in survival follow-up period and 30 days post treatment:
  - AEs/SAEs only if related to the study drug
  - Concomitant medications in patients with related SAEs
  - Subsequent antineoplastic therapy assessment
  - Survival status

4.2 Scientific Rationale for Study Design

ARASEC is a US-based open-label trial with an external control arm, in which men with mHSPC will be enrolled to receive treatment with darolutamide plus ADT. Participants in the darolutamide plus ADT arm will be compared with a matched external control arm derived from the ADT alone arm from the randomized phase 3 clinical trial, CHAARTED, which was also entirely conducted in the US (Kyriakopoulos *et al.* 2018, Sweeney *et al.* 2015). The study design and approach for ARASEC considers both clinically relevant and practical factors such as availability of participant-level data.

Darolutamide, added to ADT has demonstrated a significant benefit and a favorable safety profile in nmCRPC and therefore, it is expected that darolutamide in addition to ADT will enhance the disease control and will provide a significant benefit in patients with mHSPC compared to ADT alone, without increasing the incidence of key AEs.

The ongoing double blind, placebo-controlled phase 3 randomized trial (ARASENS) evaluates whether darolutamide improves overall survival in participants with mHSPC who receive darolutamide in combination with docetaxel for up to six cycles in addition to ADT compared to placebo + docetaxel plus ADT. There is no planned or ongoing study with

darolutamide added to ADT in the USA in men with mHSPC. Therefore, the present study is designed to evaluate the efficacy and safety of darolutamide in addition to ADT compared to ADT alone in participants with mHSPC.

The primary objective of ARASEC is to show that darolutamide in combination with ADT is superior to ADT alone in terms of PFS.

In the recent pivotal trials in HSPC, rPFS has been used as the sole primary endpoint or as part of a dual endpoint, indicating the importance of rPFS as an endpoint of clinical interest. With the publicly available CHAARTED data, however, using rPFS as a primary endpoint is not optimal for two reasons.

1. Radiographic disease assessment was not consistently performed in the CHAARTED trial and was required at baseline, time of development of CRPC and/or as clinically indicated. Furthermore, when dealing with historical time bias inherent in an external control from a previous clinical trial, the extent to which post-progression treatment patterns have changed since the time of the trial is an important consideration for considering an endpoint more proximal than OS. The observed post progression treatment patterns since CHAARTED demonstrates that these are likely to be different than those observed during the time of the CHAARTED trial, supporting the use of a more proximal endpoint in ARASEC.

2. It may not be possible to differentiate rPFS from reported PFS (Bayer is following up on the possible availability of data elements that might make this distinction possible).

Furthermore, given the increasing possibilities of therapy sequencing in clinical trials once participants progress to metastatic disease, there is an outstanding question as to whether an isolated evaluation of OS reliably addresses the benefit attributable to a single agent in participants with mHSPC (Aziz *et al.* 2015). Time trend biases are expected to be minimal with the primary endpoint PFS, given that new therapeutic options are only made available to participants upon progression. In addition, we are planning to conduct a real-world study to examine differences in participant characteristics and outcomes pre and post CHAARTED study. The final concept for this study can be made available for review.

4.3 Justification for Dose

Darolutamide and LHRH agonists/ GnRH antagonists are marketed products.

Based on the USPI, the recommended dose is 600mg (two film-coated tablets of 300mg) darolutamide taken twice daily, with food, equivalent to a total daily dose of 1200mg. Oral administration of darolutamide given as a tablet together with food, has a bioavailability of approximately 60-75% of the administered. Following repeated oral administration of 600 mg (2 tablets of 300 mg) bid to nmCRPC participants in ARAMIS, peak plasma concentrations of darolutamide of 4.79 mg/L (coefficient of variation: 30.9%) were reached around 4 hours after administration.

The steady-state of its two diastomers is reached after 2 to 4 days following repeated twice-daily dosing. Darolutamide is eliminated with an effective half-life of 20 hours.

For participants with moderate hepatic impairment and for participants with severe renal impairment, refer to the US package insert for recommended dose modifications.

4.4 End of Study Definition

The primary completion of the study will be reached when either the primary endpoint has been met or all participants have been followed (including Survival Follow-up) for at least 2 years after enrollment (unless the participant withdrew, died or was lost to follow-up), whichever is later.

Study completion will occur after closure of the Extension phase, which involves an additional year of participant follow-up after primary completion with limited data collection to support descriptive survival analyses. Following final study completion, study drug will be discontinued, and patients can transition to an available standard of care at the discretion of the investigator.

The sponsor has the right to close this study or individual sections of this study at any time.

Reasons for closure may include:

- If risk-benefit ratio becomes unacceptable.
- Safety findings from this study (e.g., SAEs).
- Results of parallel clinical studies or emerging data from literature.
- Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; dropout rate; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- For strategic reasons (e.g., the clinical development of the treatment combination is stopped).

If the trial is stopped but benefits are observed for ongoing participants, options for treatment continuation will be discussed and agreed between the investigator, sponsor and the participants.

5. Study Population

The study population includes participants with a diagnosis of metastatic hormone sensitive prostate cancer (mHSPC).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be ≥ 18 years of age inclusive, at the time of signing the informed consent.
2. Participants must have histologically or cytologically confirmed adenocarcinoma of the prostate. Participants may have begun androgen-deprivation therapy (up to 120 days prior to enrollment).
   Note: Relugolix is not permitted as ADT in this study. Relugolix is permitted prior to first screening visit, as long as it is switched to an alternative ADT prior to enrollment.
3. Participants must have metastatic disease and will be stratified by presence of high volume or low volume disease. Low volume disease is defined as any metastatic disease that is not high-volume disease.
   High volume disease is defined as:
   - Visceral Metastases (extranodal)
     AND/OR
   - Bone Metastases
     At least 4 or more bone lesions, one of which must be outside of the vertebral column AND pelvis.
4. Documented measurable metastatic disease, which includes bone lesions detected by positive 99mTc-bone scan, and/or measurable soft tissue or visceral metastases (per RECIST v1.1), detected by contrast enhanced abdominal/pelvic/chest computed tomography (CT) or magnetic resonance imaging (MRI) scan.
   NOTE: Radiographic studies identifying measurable or non-measurable disease must be obtained according to the following criteria:
   - If androgen deprivation therapy has not commenced prior to enrollment, scans must be obtained within 6 weeks of enrollment.
   - If androgen deprivation has commenced prior to enrollment,
     - Scans must be obtained within 6 weeks prior to the start of androgen deprivation therapy.
     - If all required imaging had not been completed prior to starting androgen deprivation, then any additional scans must be obtained after starting androgen deprivation but prior to enrollment. (It is assumed the scans of participants with high volume disease would not normalize in less than 120 days to the point a participant would go from “high volume” to “low volume”).
   - Superscans are allowed if they show evidence of measurable soft tissue disease.
5. Eastern Clinical Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2.
   (NOTE: Participants with PS 2 are only eligible if the decline in PS is due to metastatic prostate cancer).

6. Participants must have adequate organ function within 4 weeks prior to enrollment and evidenced by:
    a. Absolute Neutrophil Count ≥ 1500/mm^3
    b. Platelet count ≥ 100,000/mm^3
    c. Total bilirubin ≤ 1.5 ULN (except for participants with Gilbert's Disease)
    d. ALT/AST ≤ 1.5 X ULN
    e. Creatinine ≤ 2.0 X ULN
    f. Creatinine clearance (CrCl) of ≥ 30 mL/min. CrCl should be calculated at screening using the Cockcroft-Gault formula: creatinine clearance for males (mL/min) = (140 - age) (body weight in kg)/[72 x (serum creatinine in mg/dl).
    g. PTT, PT, INR ≤ 1.5 x ULN (except if on therapeutic anticoagulation in which case the participant can be enrolled if stable and anti-coagulation levels are appropriate for their condition per good clinical practice).
7. At least 4 weeks since prior major surgery and recovered from all toxicity from such surgery prior to enrollment.
8. Prior adjuvant or neoadjuvant hormonal therapy allowed provided the following criteria are met:
    - Therapy was discontinued ≥ 12 months ago AND there was a clinical state without evidence of disease at least 12 months after completing adjuvant or neoadjuvant hormonal therapy, as defined by 1 of the following:
        - PSA < 0.1 ng/mL after prostatectomy plus hormonal therapy
        - PSA < 0.5 ng/mL and has not doubled above nadir after radiotherapy plus hormonal therapy
    - Therapy lasted no more than 24 months.
9. Prior palliative radiotherapy allowed for participants, if commenced prior to starting androgen deprivation.
10. Bicalutamide, nilutamide or flutamide are allowed as single-agent therapy ≤ 28 days before medical castration to prevent flare.
11. During the treatment period and for at least 1 week after the last dose of study treatment, sexually active male participants must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol and refrain from donating sperm during the treatment period and for at least 1 week after the last dose of study treatment.
12. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. PSA level has risen and met criteria for PSA progression (as defined in Section 3) from its lowest point between the beginning of androgen deprivation therapy and enrollment.
2. Prior history of malignancy in the past 5 years, with the exception of basal cell and squamous cell carcinoma of the skin.

3. Active cardiac disease defined as having had any of the following within 6 months prior to start of treatment: myocardial infarction, severe/unstable angina pectoris, congestive heart failure, hospitalization for any cardiac event, including conduction abnormalities.
4. Pathological finding consistent with small cell, or neuroendocrine carcinoma of the prostate.
5. Known brain/ leptomeningeal metastases.
   Note: Brain CT/MRI scan should be performed only in case of symptoms.
6. An active viral hepatitis (defined as Hepatitis B surface antigen [HBsAg] reactive or detectable [qualitative] HBV DNA defined as HCV Ribonucleic Acid [RNA] [qualitative] is detected), known human immunodeficiency virus infection with detectable viral load, or chronic liver disease with a need of treatment.
   Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local authority. No HIV testing is required unless mandated by local authority.
7. Uncontrolled hypertension as indicated by a resting systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite medical management.
8. A GI disorder or procedure which is expected to interfere significantly with absorption of study treatment.
9. 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.
10. Participants with prior hormone therapy in the metastatic setting.
11. Participants with any prior chemotherapy in the adjuvant, neoadjuvant or metastatic setting for treatment of prostate cancer (including chemotherapy used to treat other types of cancer, which has proven efficacy in prostate cancer as well).
12. Concurrent use or previous exposure of 5-alpha reductase inhibitors (within 28 days before the start of darolutamide or 5 half–lives of the drug, whichever is shorter).
13. Any Prior treatment with:
    - Second–generation androgen receptor (AR) inhibitors such as enzalutamide, apalutamide, darolutamide, or other investigational AR inhibitors, Cytochrome P17 enzyme inhibitor such as abiraterone acetate or other investigational CYP 17 as antineoplastic treatment for prostate cancer.
14. Previous (within 28 days before the start of darolutamide 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).
15. Contraindication to both CT and MRI contrast agent.
16. Known hypersensitivity to any of the study treatments, study treatment classes, or excipients in the formulation of the study treatments.
17. Inability to swallow oral medications.
18. Refusal to sign informed consent.

5.3 Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and any serious adverse event (SAE).

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened within the 28-days screening period, after approval by Study Medical Monitor. Lab tests may be repeated once within the 28-day screening period, without needing to formally rescreen the participant. This should also be approved by the Study Medical Monitor and Sponsor. Rescreened participants will be assigned a new participant ID via the IWRS.

Re-screening of screen failed participants may only be allowed once after discussion with the Study Medical Monitor and the Sponsor. Sponsor approval of re-screening for a screen failed participant must be documented.

The participants who need to repeat the screening procedures will be re-consented.

Investigator must ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk.

6. Study Treatment

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Treatment Administered

Participants will receive darolutamide 600 mg (2 tablets of 300 mg) administered twice daily with food, until clinical progression (as defined in Section 3), unacceptable toxicity, withdrawal of consent, participant's or investigator's decision to stop therapy for the participant, sponsor's decision to terminate the study, or death.

Note: participants who experience a clinical benefit may continue the study treatment beyond clinical progression, at investigator's discretion. The decision must be documented in electronic case report forms (eCRF).

See Table 6-1 for further details of darolutamide administration.

Table 6-1: Administration of study treatment

Study Treatment	Darolutamide
Dosage Level(s)	**Darolutamide** Darolutamide 600 mg (2 tablets of 300 mg) will be administered twice daily with food, equivalent to a total daily dose of 1200 mg.
Route of Administration	**Darolutamide:** Oral (p.o.)
Use	**Darolutamide:** Experimental
IMP and NIMP	**Darolutamide:** IMP
Sourcing	**Darolutamide:** Provided centrally by the sponsor.
Packaging and Labeling	**Darolutamide:** White opaque wide-necked high-density polyethylene (HDPE) bottles closed with white opaque screw cap polypropylene (PP) / PP with seal polyethylene child-resistant. Each container will be labeled as required per country requirement.

Abbreviations: ADT = androgen deprivation therapy; LHRH = luteinizing hormone-releasing hormone; HDPE = high-density polyethylene; PP = polypropylene; IMP = Investigational Medicinal Product; NIMP = Non-Investigational Medicinal Product.

ADT Background Treatment

All participants will receive and remain on a stable regimen of ADT (LHRH agonist /GnRH antagonists or surgical castration, type of ADT at the discretion of the investigator). ADT will be provided locally by the trial site.

The ADT (LHRH agonist/GnRH antagonist or orchiectomy) with or without first generation antiandrogen, should be started within 120 days before enrollment. For participants who did

not undergo surgical castration, concurrent treatment with a LHRH agonist/GnRH antagonists must be documented in the eCRF.

The choice of the LHRH agonist/ GnRH antagonist will be at discretion of the Investigator. The dose and schedule of administration will be consistent with the local prescribing information approved.

Note: Relugolix is **not** permitted as ADT in this study. Relugolix is permitted prior to first screening visit, as long as it is switched to an alternative ADT prior to enrollment.

Antiandrogens (e.g., bicalutamide or flutamide) may be used in addition to androgen-deprivation therapy but may not be used as the sole hormonal therapy. Anti-androgens combined with 5-alpha reductase inhibitors are also not allowed as sole therapy. An investigator may administer this class of drug as a single agent ≤ 28 days before medical castration to cover the testosterone surge associated with LHRH agonists. The 120-day window of androgen-deprivation or hormonal therapy starts with commencement of either the antiandrogen or LHRH therapy.

6.2 Preparation/Handling/Storage/Accountability

Darolutamide should be stored in the original container not above 30°C as indicated on the clinical supply label.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all darolutamide received and any discrepancies are reported and resolved before use of the darolutamide.
2. Only participants enrolled in the study may receive darolutamide and only authorized site staff may supply or administer darolutamide. All darolutamide must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for darolutamide accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused darolutamide are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are not applicable for this study. All participants will be enrolled in the study using an Interactive Web Response System (IWRS) for tracking purposes.

Before the study is initiated, the log in information & directions for the IWRS will be provided to each site. Returned darolutamide should not be re-dispensed to the participants.

Darolutamide will be provided by the sponsor at the study visits summarized in SoA (Section 1.3).

6.4 Study Treatment Compliance

When participants self-administer darolutamide at home, compliance with study treatment will be assessed at each visit. Darolutamide accountability will be performed by the

designated study staff at each visit. Deviation(s) from the prescribed dosage regimen should be recorded in the Drug Accountability Form.

6.5 Concomitant Therapy

Any concomitant medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

All concomitant treatments from the time of the informed consent (IC) until the EOT visit must be recorded on the CRFs. Once the participant has been withdrawn from the treatment with darolutamide, follow–up treatments will be recorded if used to treat new study treatment–related SAEs or unresolved related AEs or if being used as a systemic antineoplastic therapy for prostate cancer.

6.5.1 Permitted concomitant therapy

Analgesic use will be captured in eCRF. Investigators or designees are to record which opioid and non-opioid medications were used since the last visit.

Palliative radiation therapy or surgical intervention as needed (for pain/symptom control) are allowed during study treatment. The reason for palliative radiation therapy or surgical intervention will be recorded. If such therapy or intervention is assessed to be related to clinical progression, the participant will be discontinued from treatment, as described in Section 7.1.

Participants should be evaluated by investigators for presence of osteoporosis according to local guidelines and be provided with bone treatment support per local standard of care. Participants receiving treatment with osteoclast-targeted therapy at a dose and schedule indicated for osteoporosis / prophylaxis for skeletal events prior to study entry only, may continue treatment at the same dose and schedule.

Switching an LHRH agonist to an GnRH antagonist is permitted during study treatment, the reason and the time of LHRH treatment modification must be documented in the eCRF.

See USPI for details of drug-drug interactions.

6.5.2 Prohibited concomitant therapy

In terms of drug-drug interaction darolutamide is a substrate of CYP3A4 and P-glycoprotein (P-gp). Therefore, the use of strong CYP3A4 inducers and P-gp inducers (e.g., carbamazepine, phenobarbital, St. John's Wort) during treatment with darolutamide is

not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.

In addition, darolutamide is an inhibitor of Breast Cancer Resistance Protein (BCRP).

This indicates that co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP substrates (e.g., methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the related recommendation in the product information of the BCRP substrate should be followed when co-administered with darolutamide.

Please consult the USPI for details of drug-drug interactions.

Concomitant treatment with another systemic anticancer therapy or another investigational medicinal product is prohibited with the exception of ADT throughout the study after enrollment. ADT selection should be per PI discretion.

Initiation of the following medications/treatments during the study treatment period is prohibited:

- Any investigational medicinal product
- Radiopharmaceuticals
- Immunotherapy and immune-oncology agents
- Cytotoxic chemotherapy
- Enzalutamide, Apalutamide
- Abiraterone acetate, TAK–700, or other CYP17 inhibitors
- Systemic ketoconazole
- Use of bone health agents (bisphosphonate or denosumab) to prevent skeletal related events should be assessed before or at the time of enrollment; use of these agents for prevention of skeletal-related event are not allowed after enrollment, until after a skeletal related event occurs or after a participant develops hormone refractory disease.

Any new systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of darolutamide.

For prohibited prior therapy, please refer to exclusion criteria (Section 5.2).

6.6 Dose Modification

For dose modifications, refer to the US Prescribing Information for darolutamide. In addition, if Grade ≥3 study treatment-related adverse event occurs while the participant is on a dose of 300 mg bid (following temporary or permanent dose reduction), the participant must be withdrawn from treatment with darolutamide.

For toxicities considered by the investigator to be not related to study treatment, but clinically significant, the decision to interrupt or reduce the dose is left to investigator’s decision.

Toxicities will be graded using the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI–CTCAE) v. 5.0. All dose modifications regardless of relatedness should be recorded on the eCRF.

If a participant experiences several study treatment–related toxicities with different grading, the recommendation of the worst grading should be used. If a dose of darolutamide is delayed, the dose can be taken up to 6 hours later with food to make up for the missed one.

Participants who experience hepatic transaminase elevations suggestive of idiosyncratic drug induced liver injury (DILI) considered to be causally related to study drug should discontinue study drug. Please see Section 7.1.

6.6.1 Dose interruption

The maximum duration for a dose interruption of darolutamide is 28 consecutive days. Any participant requiring dose interruption > 28 consecutive days must be withdrawn from treatment with darolutamide.

6.6.2 Dose reduction

For dose reductions, refer to the US Prescribing Information for darolutamide.

6.6.3 General requirements for dose modifications of study drug

A participant who experiences a Grade 2, 3 or 4 TEAE that is thought to be related to study drug, should interrupt study drug until the TEAE improves to < Grade 2 or to baseline status.

Cases of idiosyncratic drug-induced liver injury (DILI) with increases in ALT and/or AST to ≥ 5 and ≥ 20 x ULN, including with concomitant bilirubin elevation > 2x ULN, have been reported with darolutamide. Liver function tests abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug, should discontinue study drug.

Additional lab tests monitoring is recommended for Grade 2 or higher ALT and/or AST increase (ALT/AST > 3 x ULN). Please see the below Table 6-2.

Table 6-2 Study drug dose modification

Type of AE and Severity grade (NCI-CTCAE v 5.0)	Dose modification	Study treatment withdrawal
All AE except ALT/AST increase		
Grade 0-2	Treat on time. Per investigator's decision whether to reduce or interrupt the study drug. [a,b]	
Grade 3 or 4	Interrupt until ≤Grade 2 or baseline. [a] When the severity is ≤ Grade 2 or baseline, restart a reduced dose of 300 mg bid. [b,c]	If Grade ≥3 study drug-related TEAE occurs while the participant is on a dose of 300 mg bid (following temporary or permanent dose reduction) the participant must be withdrawn from treatment with study drug
AE: ALT/AST increase		
Grade 0-1	Treat on time. Per investigator's decision whether to reduce or interrupt the study drug [a]	
Grade 2-3-4	**If ALT or AST rise to >3 ULN:** Per investigator's decision whether to reduce or interrupt the study drug. [a] Monitor LFT (ALT, AST, total and direct bilirubin, ALP) and INR within 72 hours after the onset and then as frequently as needed according to Investigator's clinical judgment, until ALT and/or AST returns to baseline or normal values.	**If ALT or AST rise to >3 ULN:** Participants must be discontinued from the study treatment in case of hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug. DILI should be suspected after other causes of liver injury, have been excluded. Please see Section 10.3.5 for further guidance. Criteria for study treatment discontinuation (FDA 2009): • ALT or AST >8 x ULN • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN and (TBL >2 x ULN or INR >1.5) • ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
All grades **Further recommendations**	• If ALT and AST return to normal values or to baseline after study drug interruption, study drug may be restarted at the reduced dose of 300 mg bid • If, at the reduced dose, there is no increase of ALT or AST in the subsequent two weeks, full dose may be resumed. • If, at the reduced or full dose, ALT or AST values rise again, study drug should be permanently discontinued. Monitor LFTs until ALT and/or AST return to baseline or normal values.	

Abbreviation: AE, Adverse events; bid, Twice daily; ALP, Alkaline phosphatase; NCI-CTCAE v 5.0, National cancer institute-Common terminology criteria for adverse events version 5.0; TEAE, Treatment emergent adverse event.

a. If there is no recovery after 28 consecutive days, treatment with study drug should be permanently discontinued.
b. When AE returns to baseline or is resolved, re-escalation to 600 md bid may be considered by the investigator.

c. If, following a re-escalation to 600 md bid a second Grade ≥3 study drug TEAE occurs, a permanent dose reduction to 600 mg bid is required. A third occurrence of a Grade ≥3 study drug related TEAE requires permanent discontinuation of treatment with study drug.

Note: table excludes clinically non-significant and asymptomatic laboratory abnormalities.

6.7 Treatment after the End of the Study

Following final study completion, defined as one year post-primary completion, study drug will be discontinued and patients can transition to an available standard of care at the discretion of the investigator. However, the sponsor reserves the right to terminate access to darolutamide, in particular if the study is terminated due to safety concerns or lack of proven efficacy.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

All participants who enter the study should complete all applicable study periods. Participants can be withdrawn from any study period at any time. Withdrawal from the treatment period alone does not constitute withdrawal from the study.

Participants who withdraw from the treatment period for any reason are to be encouraged to remain on the study for follow-up of primary, secondary and other objectives (i.e. continue in the active follow-up and survival follow-up periods). Participants are expected to participate in Active Follow-up unless they explicitly object. Withdrawal of consent to the treatment period should be documented in the participant's medical record. If the participant does not wish to be followed up further, this additional consent withdrawal for follow-up must also be documented.

7.1 Discontinuation of Study Treatment

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If darolutamide is definitively discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of darolutamide, in follow-up, and for any further evaluations that need to be completed.

If a clinically significant finding is identified, including, but not limited to:

- changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented.
- drug-induced liver injury (DILI): participants must be discontinued from the study treatment if hepatic transaminase elevations suggestive of idiosyncratic DILI are observed considered to be causally related to study drug. (See Appendix 3, Section 10.3.5).

Any new clinically relevant finding should be reported as an AE.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant must be withdrawn from the study at any time at his own request.
- A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, and additionally requests destruction of her/his samples taken but not yet tested, the investigator must document this (destruction by site or request to lab, as applicable) in the site study records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit* as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

*Note: Rescheduled visits may be performed using the remote visit option (See Section 8).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Note: If the study participant is not able to come to the investigational site for protocol-specific visits, alternative methods for assessments (e.g., phone contact, virtual visit, alternative location for laboratory tests and imaging, provided that the imaging modality is consistent for a particular participant throughout the study) should be implemented when necessary and feasible as per local health authority and ethic committees. Darolutamide, typically distributed for self-administration, is also amenable to alternative secure delivery methods from the site pharmacy.

8.1 Efficacy Assessments

Refer to the SoA (Section 1.3) for detailed timing of efficacy assessments.

All participants should be evaluated as metastatic at screening scans, as confirmed by the investigator. Participants will have tumor evaluation by conventional methods including 99mTc-phophonate whole body bone planar scans (the preferred radiotracer is 99mTc-methylene diphosphonate [99mTc-MDP] but other commercially available 99mTc-phosphonate radiotracers such as hydroxymethylene diphosphonate [HMDP] or hydroxyethylene diphosphonate [HDP] or 2,3-dicarboxypropane-1, 1-diphosphonate [DPD] may also be used in accord with local site practice) and CT scans and/ or MRI at baseline and then at any time according to standard of care practice in the case of PSA progression, symptomatic progressive disease, or change of antineoplastic therapy or if recommended as part of standard of care procedure.

Beyond screening assessment, there are no study specific requirements for tumor imaging assessments and all scans should be performed as per local standard of care practice.

Participants should be followed with the same imaging method used at baseline (Section 1.3). The same technique (e.g., slice thickness, field of view) should be used for all scans during the study treatment period. Preferably all scans should be interpreted by the same investigator/radiologist during the study whenever possible.

If a participant develops contraindication to CT contrast media during the course of the study after the baseline imaging, contrast enhanced MRI shall be performed. In rare cases where the

participant develops contraindication to both CT and MRI contrast media, the post–baseline imaging examination could continue without contrast media.

Radiographic progression by soft tissue/visceral lesions is assessed according to RECIST criteria, version 1.1, based on MRI / CT scans of the chest, abdomen, and pelvis, as recommended by Prostate Cancer Clinical Trials Working Group (PCWG3).

Radiographic progression by bone lesions is assessed according to PCWG3 criteria based on whole body 99mTc-phophonate whole body bone planar scans. Bone lesions will be recorded separately from soft tissue/visceral lesions.

The endpoint of Radiographic progression will be based on investigator assessment. However, all participant scans (CT/MRI and bone scans) throughout the study should be saved and submitted to the sponsor in digital format, so that an independent central review can be performed if needed. Details regarding the scans to be submitted and the details process for submission can be found in the site imaging manual.

Malignant Disease Evaluation

To assess radiographic progression, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion. All measurements should be recorded in metric notation.

The term *evaluable* in reference to measurability will not be used because it does not provide additional meaning or accuracy. At baseline, tumor lesions/lymph nodes will be characterized as either measurable or non-measurable.

Definition of measurable disease

- Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease:

All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable. Previously treated lesions can only be selected as target lesions when they have progressed prior to baseline.

Cystic lesions:

- Lesions that meet radiographic criteria for simple cysts should not be considered malignant lesions (neither measurable nor non-measurable).
- "Cystic lesions" thought to be cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. However, if non-cystic lesions are present in the same participants, these should be preferably selected for assessment.

Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and their suitability for accurate repeated measurements.

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference.

Radiographic progression: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

All other lesions (or sites of disease) including pathological lymph nodes (with short axis ≥ 10 mm and < 15 mm) not considered as target should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.

Radiographic progression by bone lesions is assessed according to PCWG3 criteria based on whole body 99mTc-phophonate whole body bone planar scans (the preferred radiotracer is 99mTc-methylene diphosphonate [99mTc-MDP] but other commercially available 99mTc-phosphonate radiotracers such as hydroxymethylene diphosphonate [HMDP] or hydroxyethylene diphosphonate [HDP] or 2,3-dicarboxypropane-1, 1-diphosphonate [DPD] may also be used in accord with local site practice). Bone lesions will be recorded separately from soft tissue/visceral lesions. Bone lesions detected by CT or MRI should not be recorded as bone lesions.

PFS

PFS will be assessed from enrollment to PSA progression, clinical progression, or death, whichever occurs first. Clinical progression is defined as increasing symptomatic bone metastases, radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases, or clinical deterioration due to cancer per investigator's opinion.

PSA-related endpoints

PSA progression is defined in Section 3. For PSA-related endpoints (PFS, time to CRPC, and PSA response rate at 6 months from enrollment), PSA values obtained by local laboratory will be used.

Radiographic progression-free survival (rPFS)

rPFS will be assessed from the time of enrollment as defined in Section 3.

Overall survival

Overall survival will be assessed for all participants who are alive at the time of primary endpoint data cutoff until End of Study.

8.2 Safety Assessments

Safety will be assessed by monitoring and recording all AEs and SAEs, cardiac, hematologic, and blood chemistry parameters, vital signs, ECOG PS, and any abnormal findings observed during the performance of physical examinations.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing information (e.g., for protocol-specified procedures). The specific information (e.g., explanation of the basis of the missing data) will be captured in the case report form and the information will be summarized in the clinical study report. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

Missing information will be recorded as a protocol deviation(s) and summarized in the Clinical Study Report.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological systems. Height and weight will also be measured and recorded, as outlined in the SoA (Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Temperature, heart rate and blood pressure will be assessed.

- Blood pressure and heart rate measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and heart rate measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 10 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate.

8.2.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. If a participant has an ECG with a QTcF > 500 ms, this is to be confirmed by another ECG taken 1-2 hours later. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Note: Androgen deprivation therapy may prolong the QT/QTc interval; therefore, a periodic monitoring of electrocardiograms and electrolytes, especially in participants with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in participants taking drugs known to prolong the QT interval should be considered.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
    - The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of darolutamide should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant

management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendices 10.3.1 and 10.3.2, respectively.

If disease progression leads to clinical signs and symptoms that meet the criteria for seriousness, these events, not the underlying cause, should be reported as an AE.

Disease progression per se should not be reported as an AE. Instead, the associated signs and symptoms should be reported as AEs. In case of disease progression resulting in death, the cause of death should be reported and not disease progression.

The intensity of AEs should be documented using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, v. 5.0) (Section 10.5).

The study treatment action should be recorded separately for each study treatment as detailed in the CRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs, considered related to the study treatment or study procedures, or those that caused the participant to discontinue the study treatment or the study (see Section 7).

Investigators should refer to the current darolutamide Investigator's Brochure and LHRH agonists/GnRH antagonists product information for the expected adverse reactions. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF) until 30 (+7) days after the last darolutamide treatment at the time points specified in the SoA (Section 1.3). Any SAE judged by the investigator to be related to the study treatment should be reported until the event is resolved or stabilized, or until the end of study as defined in Section 4.4.

All AEs will be collected from the signing of the ICF until 30 (+7) days after the last darolutamide treatment, at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before obtaining informed consent will be recorded on the medical history section of the case report form (CRF).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the case report form (CRF).

Medical occurrences that started before but deteriorated after obtaining informed consent will be recorded as adverse events.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from becoming aware of the event, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Once data regarding survival and remission status are no longer required by the protocol, only second primary tumors regarded as related to study treatment should be reported.

Recurrence or metastatic disease should not be reported as an AE or SAE.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements

relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those using medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Sexually active male participants must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the study treatment and for 1 week after the end of the treatment with darolutamide.

Pregnancies inadvertently fathered by study participants during the study should be reported and followed up by the investigator using the Bayer Pregnancy Monitoring Forms, if permissible by local legislation.

For a pregnancy in the partner of a male study participant in the active treatment of the study, all efforts will be made to obtain similar information on course and outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period, subject to the partner's consent.

Pregnancies will be collected from the date of the IC signature until 30 days after the last dose of darolutamide is administered.

If an adverse outcome of pregnancy is suspected to be related to study treatment exposure, this should be reported regardless of the length of time that has passed since the exposure to the study treatment.

An induced or a spontaneous abortion is considered to be SAE and should be reported in the same timeframe and in the same manner as all other SAEs.

For all reports, the forms provided are to be used. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

8.3.6 Adverse Events of Special Interest

There are no adverse events of special interest in this study.

8.4 Treatment of Overdose

The highest dose of darolutamide studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity.

In the event of intake of a higher than recommended dose, treatment with darolutamide can be continued with the next dose as scheduled.

There is no specific antidote for darolutamide and symptoms of overdose are not established.

No specific information is available on the treatment of overdose of darolutamide. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Clarification as to intentional or accidental overdose should be reported.

In the event of an overdose, the investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
2. Any overdose or incorrect administration of study treatment should be noted on the Study Drug Administration electronic Case Report Form (eCRF).
3. Adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.*

For detailed guidance on overdosing please refer to the most current version of the IB for darolutamide.

*Note: Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant, consultation with the Medical Monitor should be considered as needed.

9. Statistical Considerations

Analyses to evaluate the efficacy and safety of darolutamide in combination with Androgen Deprivation Therapy (ADT) versus ADT alone as treatment for men diagnosed with Metastatic Hormone-sensitive Prostate Cancer (mHSPC) are described. The study will use a matched control arm from the ADT alone arm from the CHAARTED trial. The matching will be conducted by analysts who are blinded to the post-baseline efficacy outcome data and the actual use or dosing of the ARASEC study.

9.1 Statistical Hypotheses

The primary hypothesis of this study is that darolutamide in combination with ADT is superior to ADT alone in terms of progression-free survival (PFS) by testing the following null hypothesis under the proportional hazards model against an alternate of a hazard ratio less than 1 using a one-sided alpha level of 0.025.

$$H_0: h_A(t)/h_C(t) \geq 1 \text{ vs } H_1: h_A(t)/h_C(t) < 1,$$

where $h_A(t)$ and $h_C(t)$ are the hazards over time t in the matched ARASEC and CHAARTED control arms.

9.2 Sample Size Determination

Assuming a one-sided alpha of 0.025, power of 90%, and a hypothetical enrollment ratio of 1:1 between the experimental and external control arms, approximately 161 PFS events across the two arms are required to detect an increase in median PFS relative to the matched control, if the hazard ratio is 0.60. With exponential distribution, this hazard ratio translates into a 66% increase in PFS (from 11.6 months to 19.3 months).

A total of 200 participants will be enrolled to receive darolutamide plus ADT to account for dropouts and mismatches and matched with 394 external control arm participants with a 1:1 ratio. This matching will be conducted by analysts using baseline data who are agnostic to ARASEC outcomes. Assuming a final match rate of ~80%, approximately 160 participants per arm (a total of 320 participants) will be available in the matched population for the endpoint comparisons. Additional participants may be enrolled in the event of a lower matching rate.

The sample size calculations provided here are based on the above-mentioned expectations. The actual sample size and matching ratio may differ if a larger number of participants have baseline profiles different from those available in CHAARTED. Any such changes will be made before the unblinding of the ARASEC outcome data to analysts and will retain the specified one-sided 0.025 level false positive rate.

The expected study duration for the PFS endpoint is 27 months, assuming participants are enrolled approximately at a rate of 15 participants per month, and an enrollment ramp-up time of 3 months. An additional follow-up of one year is expected before the assessment of the rPFS endpoint. These durations are longer in the CHAARTED control, (Sweeney *et al.* 2015) where the accrual period for the study extended from July 2006 to December 2012, a period of 6.5 years. The Datasphere data contains data till December 2014 on the primary endpoint, yielding 2 years of potential follow-up data for the last participant enrolled. To provide a

control cohort comparable to the ARASEC cohort at a cut-off point, we will obtain from the matched ARASEC cohort, the maximum potential follow-up time *f* for the last participant enrolled and the total accrual time *a*. Hence, all participant follow-ups would be distributed between *f* and *f+a*.

Participant-wise truncated follow-ups will be sampled using fixed pre-specified seeds from the ARASEC distribution of potential follow-ups and merged into the matched CHAARTED control data. We use the word 'potential' to denote follow-up's attainable irrespective of whether the participant was actually censored or had had an event before data cut-off. The duration of time to event or censoring in the available control data will be reassessed participant-wise using truncated follow-ups. When this follow-up is less than the time to event or censoring in the control data, this duration will be reduced to the truncated follow-up and the participant will be deemed censored.

The analytical argument is like that in the computation of expected events rates when computing the sample size in time-to-event trials, such as that in (Collett 2003). The expected follow-up is given by

$$\int_0^a (f + a - t).dF(t) = \int_f^{f+a} t.dF^*(t)$$

Where *f* and *a* are as noted before and *F(t)* is the distribution of accrual times. This is equivalent to the expression using *F*(t)*, the distribution of potential follow-up's induced in the range from *f* to *f+a* through the accrual distribution. Under uniform accrual, this evaluates to *f+0.5*a*, half-way through the range. Due to the enrollment ramp-up time noted earlier and possible variation in planned enrollment rates, this expected follow-up may differ. Sampling from the distribution *F*()* for truncations to follow-up in the matched CHAARTED control, will carve out equivalent follow-up.

9.3 Populations for Analyses

The populations for analyses will be the Match Eligible Full Analysis Set (ME-FAS) and the Matched Full Analysis Set (M-FAS) as described in Table 9-1. Matching will be further defined in the SAP and will use the following baseline factors which are likely to affect the outcome and are available in the Datasphere for the CHAARTED study:

- Age
- ECOG Performance Status
- Extent of disease
  - High volume with Visceral metastasis
  - High volume with Bone metastasis only (no Visceral metastasis)
  - Low volume
- Prior Local Therapy
- Gleason Score
- Baseline PSA category (ng/mL)

These factors are considered prognostic factors and/or stratification factors in the pivotal mHSPC randomized trials (TITAN, ENZAMET, LATITUDE, STAMPEDE and ARCHES). Therefore, a matching algorithm will be employed to ensure participants are similar between the two arms regarding these measured baseline factors. The M-FA population will be the

primary population for baseline summaries and for all efficacy analyses described and will be presented together for the data items of interest shared across the two cohorts. Safety analyses for darolutamide participants in ARASEC M-FAS will be presented next to those for the ARASEC ME-FAS.

Table 9-1: Analysis populations

Population	Description
Match Eligible Full Analysis Set (ME-FAS)	Participants who sign Informed Consent and take at least one dose of darolutamide in the ARASEC cohort will be considered eligible for matching. For CHAARTED the eligible patients will be the control participants in the ITT population. In ARASEC approximately 200 participants are expected to be eligible.
Matched Full Analysis Set (M-FAS)	The M-FAS will include all participants from the ME-FAS who are matched 1:1. Participants without a match will be removed. Analysts will be agnostic to post baseline efficacy data when conducting the match.

Abbreviations: ITT = Intention to treat; M-FAS = Match full analysis set; ME-FAS = Match eligible full analysis set.

9.4 Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The Statistical Analysis Plan (SAP) will be finalized prior to the unblinding of the sponsor to the eligible participants in the M-FAS. It will include a more technical and detailed description of the matching heuristic and the statistical analyses described in this section.

All protocol specified inferential analyses for the primary and the secondary endpoint are to be conducted at primary completion, with additional analysis for overall survival and safety after the 1-year follow-up post primary completion, conducted in a descriptive manner.

9.4.1 General Considerations

The matching to determine the M-FAS will be conducted independently by an external vendor using baseline data across the two cohorts of eligible participants. The separation of the matching analysis from the outcome analyses will be achieved though the following procedure:

- Complete baseline data will be provided to the matching analysts from the CHAARTED and the ARASEC study shortly after the last ARASEC participants is enrolled after all available baseline data for enrollees has been entered and all data queries for this data has been resolved. A matching exercise will also be conducted part-way through enrollment to gauge actual matching rates in order to consider increases in enrollment in the event of a lower matching rate. No post-baseline outcome or dosing data will be shared with the matching analysts at this time.
- The matching analysts conducts a preliminary matching based on baseline factors likely to affect outcome and provides the sponsor with key aggregate baseline tables

by the preliminary matched cohorts, as well as aggregate statistics on matching diagnostics, without providing any participant level information on matching.

- The sponsor team in collaboration with the Steering Committee (SC) evaluates aggregate participant data and diagnostics and provide the analysts feedback on the adequacy of the matching and the model.
- The analysts make any changes needed and forwards the final key baseline summaries and matching diagnostics and freeze the participant level analysis data sets flagging participants in the M-FAS.

9.4.2 Primary Endpoint(s)

The primary endpoint, PFS is defined in Section 3. The PFS endpoint will be summarized using the Kaplan Meier (KM) method. Difference between matched cohorts on PFS will be tested using an unstratified hazard ratio comparing the time to progression of the ARASEC cohort to the CHAARTED cohort will be estimated from a Cox proportional hazards (PH) model. Additional details will be provided in the SAP. Inferential statistics presented will include estimates of the Hazard Ratio of ARASEC to matched Control with 95% Confidence Intervals, p-values and the median when estimable using the KM method.

9.4.3 Secondary Efficacy Endpoint(s)

The following secondary endpoints are defined in Section 3:

- Overall survival (OS)
- Radiographic Progression-Free Survival (rPFS).
- Time to castration-resistant prostate cancer (CRPC)
- Complete PSA response rate
  (The two matched cohorts will be compared on response at 6 months assessed using the Fishers Exact Test.)

All time to event endpoints will be analyzed as described for the primary endpoint.

9.4.4 Exploratory Analyses

Subgroup analyses for the primary endpoint will be provided for the baseline factors identified in Section 9.3, as well as others considered relevant and prognostic of outcome before SAP finalization, when classifications based on these are of adequate size. Analyses will be conducted using a Forest Plot plotting for each subgroup the estimated ratio of hazards of events for the matched ARASEC versus the matched CHAARTED cohorts with 95% Confidence Intervals.

9.4.5 Safety Analyses

AEs and SAEs will be coded using the latest MedDRA version at the time of database lock. The frequency and percent of all AEs/SAEs, those adverse events ≥ Grade 3 and those leading to discontinuation of study treatment will be summarized by the ARASEC M-FAS and ME-FAS groups. Descriptive summary tables will be presented on all safety parameters by these groups.

Subgroup summaries by Age Group and Race will be done for all AE's, those ≥ Grade 3 and for those leading to discontinuation of study treatment.

Other safety parameters such as ECOG PS and laboratory parameters will be analyzed in the M_FAS.

9.4.6 Sensitivity Analyses

Analyses of the primary endpoint may be conducted using alternate methods, such as those achieving balance between groups using propensity score based inverse weighting for all ME_FAS participants. Additional details will be provided in the SAP.

9.5 Interim Analyses

No interim analysis will be conducted.

9.6 Data Monitoring Committee (DMC) or other Review Board

There will be no DMC for this study.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (if acceptable by local law) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative per US regulations will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development Phases II, III, and IV and Phase I trials in participants are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases." In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov.

Bayer commits to sharing upon request from qualified scientific and medical researchers, participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the US.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator after study completion for the retention period as set forth in the Investigator Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Monitoring Plan.

10.1.8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate therapy and/or follow-up.

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g., SAEs)
    - Results of parallel clinical Bayer studies or emerging data from literature
    - Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; dropout rate; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- strategic reasons (e.g., the clinical development of the treatment is stopped)

The site is entitled to end its participation in the study if necessary due to medical or ethical reasons.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC(s)/IRB(s); competent authority (ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.

In the event of a study closure, participants on treatment and those in post-study follow-up, must be taken care of in an ethical manner.

10.1.9 Publication Policy

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1: Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
Other Screening Tests	The results of each test must be entered into the CRF.			

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CRF = Case report form; MCH = Mean corpuscular hemoglobin; MCV = Mean corpuscular volume; RBC = Red blood cell; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; WBC = White blood cell

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, which may or may not be temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For efficacy studies, include: • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. For non-efficacy studies involving marketed products in established indications, include: • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE.

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Note: Clinical importance includes need for diagnostic and treatment interventions, discontinuation of study treatment or reduction of dose, etc.

10.3.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the CRO in lieu of completion of the AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by the CRO. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the CRO. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
  Additionally, this study will grade the AEs per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v. 5.0).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the CRO. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the** CRO**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations,

Follow-up of AEs and SAEs
histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the CRO with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the CRO via an Electronic Data Collection Tool
• The primary mechanism for reporting a SAE to the CRO will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the CRO by telephone. • Contacts for SAE reporting can be found in the investigator trial file (ITF).

SAE Reporting to the CRO via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the CRO. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the investigator trial file (ITF).

10.3.5 Participant Discontinuation due to Idiosyncratic DILI

Participants must be discontinued from the study treatment if hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug are observed.

It is recommended to monitor and report in eCRF liver function tests (ALT, AST, ALP and total bilirubin) until recovery, according to your local clinical practice.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

It is not known whether darolutamide or its metabolites are present in semen. Based on its mechanism of action, darolutamide may cause fetal harm. Exposure of the fetus to an androgen receptor inhibitor through seminal transfer to the pregnant woman has to be avoided.

If the participant is engaged in sexual activity with a pregnant woman, a condom should be used during and for 1 week after completion of treatment with darolutamide.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following (as applicable) during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2.
- When having penile-vaginal intercourse with a Women of childbearing potential (WOCBP) who is not currently pregnant.
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame in Section 5.1.
- Refrain from donating sperm for the duration of the study and for the protocol-defined time frame in Section 5.1.

Table 10-2: Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods of Low User Dependency [a]

Table 10-2: Highly effective contraceptive methods

Implantable progestogen only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. As a general rule, use of hormonal contraception is not recommended if a clinically relevant interaction with contraceptive steroids has been observed or is suspected. If an interaction with contraceptive steroids has been observed or is suspected, but the effect is considered to be of limited clinical significance, the hormonal contraception method must be supplemented with a barrier method (preferably male condom).

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from both the study participant and the pregnant female partner, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy including delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Common Terminology Criteria for Adverse Events; version 5.0

Details of CTCAE grading (version 5.0) may be found:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

10.6 Appendix 6: NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer (2020)

Details of NCCN Clinical Practice Guidelines may be found in the National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer.

Available online: www.nccn.org/patients. V.1 2020.

10.7 Appendix 7: Prostate Cancer Working Group 3 Criteria

Details of the Prostate Cancer Working Group 3 Criteria may be found:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4872347/pdf/JCO642702.pdf

The modified RECIST 1.1 criteria in PCWG3 guidelines are to be used for non-bone tumor lesion assessment (e.g., visceral and lymph metastases) and the bone metastasis criteria using ^{99m} Tc-phosphonate whole body planar bone scans are to be used for assessment of bone disease. PCWG3 does advise following RECIST 1.1 (Eisenhauer *et al.* 2009) for extra-skeletal disease but also recommends the following modification: up to five lesions per site of metastatic spread (e.g., lung, liver, lymph nodes, adrenal and brain as separate sites) are to be recorded to address disease heterogeneity and to track patterns of metastatic progression. In accord with RECIST 1.1, for measurable disease in lymph nodes, only report changes in lesions ≥1.5 cm in the short axis; for visceral measurable lesions, only report changes in lesions ≥1 cm in the longest dimension. Bone lesions should be recorded separately using the bone scans. The eCRF forms provided for this trial will allow this type of recording to be made at the investigational sites.

Visceral and malignant lymph node response types as per PCWG-3 modified RECIST 1.1 criteria:

All subjects will have their best non-bone lesion response on study classified as outlined below:

- Complete Response (CR): Disappearance of all clinical and radiographic evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.
- Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. No unequivocal progression of existing non target lesions and no appearance of new lesions.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study = nadir (this includes the baseline sum if

that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute progressive disease.

- Favorable change is to be confirmed with a second CT/MRI scan.

Bone lesion response types per PCWG3:

- Bone scans will be used to assess that there are no new lesions (stable) or worse (new lesions).
- Changes in intensity of uptake alone do not constitute progression or regression.
- No new lesions would indicate continuation of therapy in the absence of other signs of progression (e.g., soft tissue progression by RECIST 1.1 above).
- For new lesions and progression, the 2x2 rule is used: at least two new lesions on the first post-treatment scan, with at least two additional lesions on the next scan. If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan. For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan and confirmed on a subsequent scan (see Figure 2 in Scher *et al.* 2016) provide a confirmed progression status.

10.8 Appendix 8: Sample list of strong CYP3A4 inducers

Strong

Ajmaline phenobarbital

Carbamazepine

Enzalutamide

Fosphenytoin

Hypericum perforatum (St. John's Wort)

Lumacaftor

Methylphenobarbital

Mitotane

Phenobarbital

Phenytoin

Primidone

Propranolol phenobarbital

Rifabutin

Rifampicin

Rifamycin

Rifapentin

10.9 Appendix 9: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 5 Protocol v.6	*02 MAY 2025*
Latest document v5.0	*19 SEP 2023*
Original Protocol	*08-DEC 2020*

Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

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