Document Type:	Study protocol
Official Title:	A randomized, double–blind, placebo–controlled Phase III study of darolutamide (ODM–201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone–sensitive prostate cancer
NCT Number:	NCT02799602
Document Date:	26-May-2020

Cover page of the integrated protocol

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

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 25 MAY 2016
- **Amendment 2** (global amendment described in Section 15.1), forming integrated protocol, Version 2.0, dated 04 OCT 2016
- **Amendment 5** (global amendment described in Section 15.2), forming integrated protocol, Version 3.0, dated 12 FEB 2018
- **Amendment 6** (global amendment described in Section 15.3), forming integrated protocol, Version 4.0, dated 10 DEC 2019
- **Amendment 7** (global amendment described in Section 15.4), forming integrated protocol, Version 5.0, dated 26 MAY 2020

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.

- **Amendment 1**, dated 20 SEP 2016 (local amendment valid for China only)
- **Amendment 3**, dated 04 NOV 2016 (local amendment valid for UK only)
- **Amendment 4**, dated 31 JAN 2017 (local amendment valid for Japan only)

1. Title page

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

Darolutamide in addition to standard androgen deprivation therapy and docetaxel in metastatic hormone–sensitive prostate cancer

Acronym: **ARASENS**

Test drug:	BAY 1841788 / darolutamide / ODM–201		
Study purpose:	Efficacy and Safety		
Clinical study phase:	III	Date:	26 MAY 2020
EudraCT: no:	2015–002590–38	Version no.:	5.0
Sponsor's study no.:	17777		

Sponsor:

a) Non–US: Bayer AG, D–51368 Leverkusen, Germany

b) US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981–0915, USA

Sponsor's medical expert:

PPD

Muellerstrasse 178
13353 Berlin, Germany
Telephone no.: PPD

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

The study will be conducted in compliance with the protocol, ICH–GCP and any applicable regulatory requirements.

Confidential

The information provided in this document is strictly confidential and is intended solely for the guidance of the clinical investigation. Reproduction or disclosure of this document – whether in part or in full – to parties not associated with the clinical investigation, or its use for any other purpose, without the prior written consent of the sponsor is not permitted.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

Signature of the sponsor's medically responsible person

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

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name: PPD Role: PPD

Date: ..... Signature: .....

Signature of principal investigator

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name:

Affiliation:

Date: _____ Signature: _____

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's Investigator site file.

2. Synopsis

Title	**A randomized, double–blind, placebo–controlled Phase III study of darolutamide (ODM–201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone–sensitive prostate cancer**
Short title	Darolutamide in addition to standard androgen deprivation therapy (ADT) and docetaxel in metastatic hormone–sensitive prostate cancer
Acronym	ARASENS
Clinical study phase	III
Study objective(s)	The primary objective of this study is: • To demonstrate the superiority in overall survival (OS) of darolutamide in addition to standard ADT and docetaxel over placebo in addition to standard ADT and docetaxel The secondary objectives of this study are to evaluate: • Time to castration–resistant prostate cancer • Time to initiation of subsequent antineoplastic therapy • Symptomatic skeletal event free survival (SSE–FS) • Time to first symptomatic skeletal event (SSE) • Time to initiation of opioid use for ≥7 consecutive days • Time to pain progression • Time to worsening of physical symptoms of disease based on functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire (NCCN–FACT FPSI–17) • Safety The exploratory objectives of this study include: • Quality of life • Medical resource use • Prostate–specific antigen (PSA) assessments • Pharmacokinetics and exposure–response analysis • Evaluate biomarkers to investigate the drug (i.e. mode–of–action–related effect and / or safety) and / or the pathomechanism of the disease
Test drug	Darolutamide (BAY 1841788)

Name of active ingredient	Darolutamide (BAY 1841788)
Dose(s)	Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.
Route of administration	Oral
Duration of treatment	Until symptomatic progressive disease, change of antineoplastic therapy, unacceptable toxicity, until subject withdraws consent, withdrawal from the study at the discretion of the Investigator or his/her designated associate(s), death, or non–compliance.
Reference drug(s)	Matching placebo
Name of active ingredient	Not applicable
Dose(s)	The dosing of placebo is the same as for darolutamide (BAY 1841788), please see above.
Route of administration	Oral
Duration of treatment	Until symptomatic progressive disease, change of antineoplastic therapy, unacceptable toxicity, until subject withdraws consent, withdrawal from the study at the discretion of the Investigator or his/her designated associate(s), death, or non–compliance.
Background treatment	ADT (luteinizing hormone–releasing hormone [LHRH] agonist/antagonist or orchiectomy) and 6 cycles of docetaxel.
Indication	Metastatic hormone–sensitive prostate cancer (mHSPC)
Diagnosis and main criteria for inclusion /exclusion	**Inclusion criteria** • Written informed consent • Males ≥18 years of age • Histologically or cytologically confirmed adenocarcinoma of prostate • Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, either by contrast–enhanced abdominal/pelvic/chest computed tomography (CT) or magnetic resonance imaging (MRI) scan assessed by Investigator and confirmed by central radiology review. Metastatic disease is defined as either malignant lesions in bone scan or measurable lymph nodes above the aortic bifurcation or soft tissue/visceral lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Lymph nodes are measurable if the short axis diameter is ≥15 mm, soft tissue/visceral lesions are measurable if the long axis diameter is ≥10 mm. Subjects with regional lymph node metastases only (N1, below the aortic bifurcation) will not be eligible for the study. Only subjects with non–regional lymph node metastases (M1a) and/or bone metastases (M1b) and/or other sites of metastases with or without

bone disease (M1c) will be eligible.

- Subjects must be candidates for ADT and docetaxel therapy per Investigator's judgment
- Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first generation anti–androgen, but no longer than 12 weeks before randomization. For subjects receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 4 weeks, prior to randomization is recommended**.** First generation anti–androgen has to be stopped prior to randomization.
- An Eastern Cooperative Oncology Group performance status of 0 or 1
- Blood counts at Screening: hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥1.5x10^9/L, platelet count ≥100x10^9/L (subject must not have received any growth factor within 4 weeks or a blood transfusion within 7 days of the hematology laboratory sample obtained at Screening)
- Screening values of serum alanine aminotransferase and/or aspartate transaminase ≤1.5 x upper limit of normal (ULN), total bilirubin ≤ULN, creatinine ≤2.0 x ULN
- Sexually active male subjects must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the treatment with darolutamide/placebo and for 3 months after the end of the treatment with darolutamide/placebo and 6 months after treatment with docetaxel.

Exclusion criteria

- Prior treatment with:
  - LHRH agonist/antagonists started more than 12 weeks before randomization
  - Second–generation androgen receptor (AR) inhibitors such as enzalutamide, ARN–509, darolutamide, other investigational AR inhibitors
  - Cytochrome P 17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as antineoplastic treatment for prostate cancer
  - Chemotherapy or immunotherapy for prostate cancer prior to randomization
- Treatment with radiotherapy (external beam radiation therapy, brachytherapy, or radiopharmaceuticals) within 2 weeks before randomization
- Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation of the study drugs
- Contraindication to both CT and MRI contrast agent
- Had any of the following within 6 months before randomization: stroke, myocardial infarction, severe/unstable angina pectoris,

	coronary/peripheral artery bypass graft, congestive heart failure (New York Heart Association Class III or IV) • Uncontrolled hypertension as indicated by a resting systolic blood pressure (BP) ≥160 mmHg or diastolic BP ≥100 mmHg despite medical management • Had a prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e., pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥5 years before randomization and from which the subject has been disease–free • A gastrointestinal disorder or procedure which is expected to interfere significantly with absorption of study drug • An active viral hepatitis, known human immunodeficiency virus infection with detectable viral load, or chronic liver disease with a need for treatment • Previous (within 28 days before the start of study drug or 5 half–lives of the investigational treatment of the previous study, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) • Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the subject and/or his/her compliance with study procedures, or may interfere with the subject's participation in the study or evaluation of the study results • Inability to swallow oral medications • Close affiliation with the investigational site (e.g., a close relative of the Investigator, dependent person [e.g., employee or student of the investigational site]) • Previous assignment to treatment in this study
Study design	Randomized, double–blind, placebo–controlled, multicenter phase III study. Approximately 1,300 subjects will be randomized (1:1 ratio) to receive one of the following study drugs: • Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg • Placebo matching darolutamide tablets in appearance, twice daily with food All subjects must receive ADT of Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, started ≤12 weeks before randomization. For subjects receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 4 weeks prior to randomization is recommended**.** Six cycles of docetaxel will be administered after randomization. Docetaxel can be administered in combination with

	prednisone/prednisolone at the discretion of the Investigator. Subjects will be stratified at randomization as follows: • Extent of disease o Non–regional lymph nodes metastases only o Bone metastases with or without lymph node metastases o Visceral metastases with or without lymph node metastases or with or without bone metastases • Alkaline Phosphatase (ALP) o ALP<ULN o ALP≥ULN Note: Blood samples to measure ALP levels for stratification will be analyzed in a central laboratory.
Methodology	The study will comprise 4 consecutive periods: Screening, Treatment, Active Follow–up, and Long–term (survival) Follow–up. **Screening period**: All trial–related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the informed consent form. The Screening period will consist of multiple evaluations that will take place within 28 days prior to randomization to ensure that all eligibility criteria are met. Once eligibility is confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with darolutamide or placebo. **Treatment period**: Study treatment will be provided for all subjects bid until symptomatic progressive disease, change of antineoplastic therapy, unacceptable toxicity, until subject withdraws consent, withdrawal from the study at the discretion of the Investigator or his/her designated associate(s), death, and non–compliance. Subjects will be evaluated every 12 weeks for castration–resistant prostate cancer, initiation of subsequent antineoplastic therapy, SSEs, opioid use for ≥7 consecutive days, pain progression, worsening of physical symptoms of disease based on NCCN–FACT FPSI–17, adverse events (AEs) and serious adverse events (SAEs), Quality of life (QoL) and PSA assessment. **Active Follow–up period:** After treatment discontinuation, subjects will enter the Active Follow–up period, which includes: • End of Treatment Visit An End of Treatment (EOT) Visit will be conducted 30 (+7) days after the last dose of study drug. The following assessments will be performed at the EOT Visit: QoL, pain assessment, analgesic consumption, subsequent antineoplastic treatments for prostate cancer (which should be provided with start and stop dates and reason for change: PSA progression, clinical

	progression, radiological progression, toxicity, or other), SSEs, and all AEs and SAEs regardless of causality. • Active Follow–up visits During the Active Follow–up period, the following assessments will be performed during standard of care clinic visits approximately every 12 weeks for up to 1 year: QoL, pain assessment, analgesic consumption, survival status, subsequent antineoplastic treatments for prostate cancer (which should be provided with start and stop dates and reason for change: PSA progression, clinical progression, radiological progression, toxicity, or other), SSEs, and study drug–related SAEs. After approximately 1 year of Active Follow–up, subjects will be transitioned to Long–term (survival) Follow–up. The Active Follow–up period extends from the discontinuation of treatment period for up to 1 year or until the subject can no longer travel to the clinic, dies, is lost to follow–up, or withdraws informed consent and actively objects to collection of further data. **Long–term (survival) Follow–up period**: After Active Follow–up, subjects will continue to be contacted approximately every 12 weeks (by phone) to capture all antineoplastic treatments for prostate cancer with start and stop date and reasons for change (PSA progression, clinical progression, radiological progression, toxicity, other), study drug–related SAEs and survival status. The end of Long–term Follow–up period is death, lost to follow–up, consent withdrawal, or end–of–study. **Survival sweep:** For every formal analysis of OS, survival data will be collected through additional survival sweeps. All subjects considered alive at the database cut-off date and prior to any subsequent additional analysis will be contacted for survival status. **After primary analysis of the study:** For subjects who are ongoing with darolutamide treatment, the sponsor will continue to provide darolutamide via a separate program at least until darolutamide is approved and reimbursed in a specific country.
Type of control	Placebo
Data Monitoring Committee	Yes
Number of subjects	Approximately 1,300 subjects in total are to be randomized
Primary variable(s)	Overall survival, defined as the time (in days) from date of randomization until death from any cause.
Time point/frame of measurement for primary variable(s)	The primary analysis will be performed when approximately 509 deaths occur in the 2 treatment arms combined. The expected study duration for 509 deaths is approximately 70 months.
Plan for statistical analysis	All randomized subjects will be included in the analysis of overall survival (OS), the primary efficacy endpoint.

	The primary efficacy endpoint of OS will be analyzed using a one–sided stratified log–rank test with an overall alpha of 0.025. Analysis will be according to treatment groups as randomized, with stratification factors extent of disease and alkaline phosphatase level. The hazard ratio (HR) (darolutamide/placebo) and its 95% confidence interval will be calculated using the Cox model, stratified by the same randomization factors. Kaplan-Meier estimates and plots will be presented for each treatment group. The secondary efficacy time–to–event endpoints will be analyzed using stratified log–rank test with randomization stratification factors. HR and 95% confidence intervals will be provided using Cox model. Interim analysis for futility at approximately 30% of total planned events will be conducted.

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

5–HT	5–hydroxytryptamine
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC	The area under the concentration–time curve
AUC(0–t_{last})	The area under the concentration–time curve from time zero to the last sample with the quantifiable concentration
AUC(0–8)	The area under the concentration–time curve from time zero to 8 h
AUC(0–12)	The area under the concentration–time curve from time zero to 12 h
AUC(0–24)	The area under the concentration–time curve from time zero to 24 h
AUC(0–72)	The area under the concentration–time curve from time zero to 72 h
AV	Atrioventricular
bid	Twice daily
BCRP	Breast cancer resistance protein
BP	Blood pressure
BPI–SF	Brief Pain Inventory – Short Form
CAB	Complete androgen blockade
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CRPC	Castration–resistant prostate cancer
CT	Computed tomography
CTC	Circulating tumor cell
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
CYP	Cytochrome P
dL	Deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EBRT	External beam radiation therapy
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status

eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
ePRO	Electronic patient reported outcome
ESMO	European Society of Medical Oncology
EU	European Union
FAS	Full analysis set
FPSI–DRS–P	FACT/NCCN FPSI–17 disease–related symptoms – physical
g	Gram
$GABA_A$	Type–A γ–aminobutyric acid
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HDPE	High density polyethylene
HR	Hazard ratio, heart rate
IB	Investigator's brochure
IC	Informed consent
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
IEC	Independent Ethics Committee
INN	International nonproprietary name
IRB	Institutional Review Board
IV	Intravenous
IXRS	Interactive Voice/Web Response System
KM	Kaplan–Meier
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
LHRH	Luteinizing hormone releasing hormone
LLOQ	Lower limit of quantification
M&S	Modeling & Simulation
mCRPC	Metastatic castration–resistant prostate cancer
mCSPC	Metastatic castration–sensitive prostate cancer
mHSPC	Metastatic hormone–sensitive prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCCN–FACT FPSI–17	Functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire

NCI–CTCAE v 4.03	National Cancer Institute–Common Terminology Criteria for Adverse Events; version 4.03
ng	Nanogram
nM	Nanomolar
OS	Overall survival
P–gp	P–glycoprotein
PCWG3	Prostate Cancer Clinical Trials Working Group
PD	Pharmacodynamic
PI	Principal investigator
PI3K	Phosphatidylinositol 3–kinase
PIK3CA	Phosphatidylinositol–4,5–bisphosphate 3–kinase, catalytic subunit alpha
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PRO	Subject–reported outcomes
PSA	Prostate–specific antigen
PTEN	Phosphatase and tensin homolog
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD	Standard deviation
SHBG	Sex hormone–binding globulin
SNP	Single gene polymorphism
SSE	Symptomatic skeletal event
SSE–FS	Symptomatic skeletal event free survival
SUSAR	Suspected unexpected serious adverse reaction
t_{last}	Time to the last quantifiable concentration
t_{max}	Time to the maximum plasma concentration
TMF	Trial master file
ULN	Upper limit of normal
UVB	Ultraviolet B
VCaP	Vertebral cancer of the prostate
WPS	Worst pain subscale

Definitions of terms

With the approval of the INN darolutamide, the Orion drug nomenclature (ODM-201) was replaced with darolutamide throughout the protocol. In addition, the Orion codes for darolutamide diastereomers and metabolite were replaced with trivial names in the entire document as shown in the table below.

	Orion name	**INN/trivial name**
Drug substance and drug product	ODM-201	Darolutamide (INN)
Diastereomer	ORM-16497	(*S*,*R*)-darolutamide
Diastereomer	ORM-16555	(*S*,*S*)-darolutamide
Metabolite	ORM-15341	Keto-darolutamide

3. Introduction

3.1 Background

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death among men worldwide (1). It is the most common non–cutaneous cancer and the second leading cause of cancer–related deaths in men in Europe (2) and the United States (3).

At the time of initial diagnosis, most men are found to have localized disease and can be treated with curative surgery or radiotherapy. However, a proportion of subjects will recur either locally or in distant sites. In addition, approximately 5% of new diagnoses present with de novo hormone–sensitive metastatic disease. The most common site of metastases is bone. However, soft tissue and visceral metastases can also occur (4). Upon development of metastatic disease, treatment is palliative, with the goal of prolonging quantity and maintaining quality of life (QoL) (5; 6; 7).

The mainstay of therapy for newly diagnosed metastatic hormone–sensitive prostate cancer (mHSPC), also known as metastatic castration–sensitive prostate cancer (mCSPC), remains androgen deprivation therapy (ADT), as recommended by the prostate cancer guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN), and the European Association of Urology (8; 9; 10). Androgen deprivation therapy can be accomplished either by surgical orchiectomy (castration) or medical castration (using either a luteinizing hormone releasing hormone [LHRH] agonist or an LHRH 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 (8; 9; 10).

Over the years, efforts have been made to improve upon ADT by modified timing (early versus deferred) and schedule (intermittent versus continuous) or by adding adjunctive agents, but the optimal management of this disease state is still not defined. Combined androgen blockade using both an LHRH agonist and an anti–androgen has been extensively studied as upfront therapy in mHSPC (6; 7; 11). 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) (12; 13; 14). According to NCCN prostate cancer guidelines 2014, CAB provides modest to no benefit over castration alone in metastatic subjects.

While ADT demonstrates antitumor activity in mHSPC with prolonged disease control, unfortunately resistance ultimately occurs and subjects die of castration–resistant prostate cancer (CRPC). Approximately 10% to 20% of prostate cancer subjects develop CRPC within 5 years, with a median time of 12–24 months (15), and have a poor median survival expectancy of 9 to 30 months (16). In the setting of metastatic castration–resistant prostate cancer (mCRPC), new therapeutic agents with different mechanisms of action have recently

become available and have significantly improved clinical outcomes, including chemotherapeutic agents (cabazitaxel), androgen–receptor targeted agents (abiraterone and enzalutamide), immunotherapies (sipuleucel–T), and radiopharmaceuticals (radium–223) (17; 18; 19; 20; 21; 22; 23). Conversely, the overall treatment paradigm of mHSPC has remained substantially stable and has not been strongly challenged until more recently, when the randomized controlled CHAARTED trial examined the addition of chemotherapy to standard ADT for metastatic hormone–sensitive disease, thus bringing chemotherapy to an arena historically dominated by hormone therapy only. The CHAARTED study demonstrated that combining 6 cycles of docetaxel chemotherapy with standard ADT was associated with a statistically significant overall survival (OS) benefit in metastatic hormone–sensitive disease compared with ADT alone, particularly in subjects with high volume disease (24; 25). Recent data from another ongoing study in Europe, the Medical Research Council STAMPEDE trial, confirm a significant OS benefit for docetaxel combined with ADT compared with ADT alone in subjects with high risk locally advanced or newly diagnosed metastatic disease (26; 27).

Chemo–hormonal therapy is currently recommended by the NCCN as first–line therapy for high volume mHSPC (11) and is recommended by ESMO Clinical guidelines as first–line treatment of metastatic, hormone–naïve disease in men fit enough for chemotherapy (33).

3.2 Overview of darolutamide (BAY 1841788)

3.2.1 Pharmacology

Darolutamide is a novel non–steroidal androgen receptor (AR) inhibitor which binds with high selectivity and binding affinity (9 nM) to AR when compared to known second-generation anti–androgens. Darolutamide is a 1:1 mixture of 2 pharmacologically active diastereomers: (*S,R*)-darolutamide and (*S,S*)-darolutamide. Diastereomers as well as the main circulating metabolite from darolutamide, keto-darolutamide, show no major differences in pharmacological activity and function as antagonists in AR–overexpressing cells.

In the vertebral cancer of the prostate (VCaP) cell line (derived from a bone metastasis of a subject with CRPC) with endogenous AR gene amplification and AR overexpression, darolutamide suppressed dose dependently androgen–induced VCaP cell proliferation more efficiently than bicalutamide.

W741L (tryptophan to leucine) mutation of AR has been shown to have a role in the mechanism of bicalutamide resistance. In this mutation, darolutamide functioned as an antagonist, whereas bicalutamide was a pure agonist, as previously shown.

In addition, darolutamide inhibits testosterone–mediated nuclear translocation of AR in AR overexpressing cells. Darolutamide and keto-darolutamide were found to decrease 0.3 nM testosterone–induced nuclear translocation at concentrations ≥100 nM and ≥300 nM, respectively; whereas bicalutamide failed to block testosterone–induced AR nuclear translocation at all tested concentrations.

In the immature rat assay, darolutamide showed anti–androgenic activity, by dose dependently and significantly antagonizing testosterone–induced growth of

androgen-sensitive tissues in ventral prostate and seminal vesicles after 6–day oral dosing, with maximal inhibition at 100 mg/kg/day.

In the castration–resistant VCaP xenograft model, darolutamide showed significant anti-tumor activity. The VCaP tumors grew significantly more slowly in mice treated with 50 mg/kg of darolutamide orally once daily for 37 days compared with untreated castrated mice, whereas tumor growth was fully inhibited after orally twice daily (bid) dosing at 50 mg/kg.

In the orthotopic prostate cancer model, where VCaP cells were inoculated into prostate of nude intact male mice, inhibition of tumor growth and reduced increase in serum prostate-specific antigen (PSA) level were observed in mice treated with 50 mg/kg of darolutamide orally twice daily for 3 weeks compared with vehicle controls. Darolutamide did not have any effect on serum testosterone levels.

3.2.2 Nonclinical pharmacokinetics and metabolism

Darolutamide is rapidly absorbed in mice and rats from preclinical formulations. Dog studies show that fasted and fed states differ in darolutamide absorption with fed states showing higher total exposure than fasted states. Upon repeated dosing, no accumulation was observed. Systemic exposure to darolutamide increased less than dose proportionally, suggesting solubility–limited absorption at the high dose levels.

Darolutamide consists of 1:1 ratio of diastereomers (*S,R*)-darolutamide and (*S,S*)-darolutamide, which are able to interconvert and exhibit different ratios in animals. In rat plasma the diastereomer ratio remains about 1:1, but mice and dogs show higher exposure to (*S,R*)-darolutamide (i.e. (*S,S*)-darolutamide is eliminated more rapidly than (*S,R*)-darolutamide in these species). (*S,S*)-darolutamide is the main human diastereomer (about 85%).

The main circulating metabolite keto-darolutamide is formed by oxidation of a secondary alcohol to form a ketone. The diastereomers (*S,R*)-darolutamide and (*S,S*)-darolutamide are able to interconvert via keto-darolutamide. In rats and dogs, the metabolite/parent darolutamide ratio is close to unity, while in mice and humans the ratio is around 2 to 3. No human–specific disproportionate metabolites have been found so far.

Systemic clearance of darolutamide in nonclinical species is low (0.2 L/h/kg in dogs) which is in agreement with the results obtained *in vitro* in hepatocyte incubations. Terminal volume of distribution of darolutamide in dogs is 1.8 L/kg.

Based on *in vitro* data, darolutamide is a substrate and inhibitor of P–glycoprotein (P–gp) and Breast Cancer Resistance Protein (BCRP). According to additional *in vitro* data, darolutamide is also an inhibitor of the uptake transporters OATP1B1 and OATP1B3. Interactions with P-gp or BCRP are expected *in vivo* based on these *in vitro* data, and also on preliminary clinical study results (please refer to Section 3.2.4).

In general, the potential for darolutamide to inhibit CYP reaction pathways *in vitro* in human liver microsomes is low. The lowest IC_{50} of 30 µM was observed for CYP2C9. For its pharmacologically active metabolite keto-darolutamide, a K_i value of 27 µM was determined. Applying a mechanistic static model, no inhibition potential towards CYP2C9 *in vivo* is expected.

The CYP450 induction potential of darolutamide and keto-darolutamide was evaluated *in vitro* in primary cultures of human hepatocytes from three individual donors. Based on these data, a risk to observe weak to moderate CYP3A4 induction by darolutamide in the clinic cannot be ruled out.

In vitro darolutamide has a free fraction of 4.5% to 8% in the plasma of human, rat, and mouse. The free fraction in dog plasma is dependent on darolutamide concentration (range: 0.3% to 11%). The major binding protein is serum albumin. There are no differences in plasma protein binding between the diastereomers. The main circulating metabolite keto-darolutamide has a free fraction <1% in most species.

Tissue distribution studies in rodents suggest that darolutamide and its metabolite keto-darolutamide have very limited access to brain (brain/plasma ratio <0.05). Prostate and heart have clearly higher tissue/plasma ratios of darolutamide. The kidney/plasma ratio of darolutamide is around 1 and the liver/plasma ratio is around 3. The results from a whole body autoradiography study in rats confirm that the ^{14}C–darolutamide–related radioactivity concentrations in tissues (except in the liver) are lower than those in plasma.

In vivo mass balance study in rats suggests that about two–thirds of darolutamide–related radioactivity is excreted to feces and the rest to urine. Maximally, 45% of darolutamide is excreted unchanged. The similar excretion pattern after intravenous (IV) and oral administration supports complete oral absorption at the studied low dose (11 mg/kg). Excretion is almost complete by 48 hours post–dose.

3.2.3 Safety pharmacology and toxicology

The repeat–dose toxicity studies with darolutamide have been conducted up to 26 weeks in the rat and up to 39 weeks in the dog. Darolutamide has been well tolerated up to the highest dose levels in both species. The no observable adverse effect level was >2 x 500 mg/kg/day in the rat and >2 x 200 mg/kg/day in the dog. All the observed effects were directly related to the anti–androgenic mechanism of action of darolutamide and no off–target toxicity could be identified in either species. The effects were also shown to be reversible after discontinuation of administration of darolutamide. Increase of exposure to darolutamide was less than dose-proportional both in rats and dogs, and no accumulation was observed. The exposure multiples of darolutamide at the highest dose level in the rat and dog were approximately up to 3–fold and 1.8–fold, respectively, compared with AUC(0–24) at the 700–mg bid dose level in subjects with mCRPC in the clinical phase I/II ARADES study (17829 / 3104001). The corresponding exposure multiples of the metabolite keto-darolutamide in the rat and dog were approximately up to 1.5–fold and 0.7–fold, respectively.

No stand–alone developmental and reproductive toxicity studies have been conducted with darolutamide. Based on the known pharmacologic effects of anti–androgens (11; 12; 13; 14), decreased fertility in males and developmental toxicity would be expected. Also it has to be taken into account that the subjects in this clinical study use gonadotropin releasing hormone agonist or antagonist treatment or have bilateral orchiectomy, which also affects fertility.

Based on the results from the completed *in vitro* and *in vivo* genotoxicity studies, darolutamide is not considered to represent any significant genotoxic risk for man. Although

both darolutamide and its metabolite, keto-darolutamide, absorb light in the UVB wavelength range of 290 to 320 nm with the absorption maximum at 290 nm, an *in vitro* 3T3 neutral red uptake phototoxicity study demonstrated that darolutamide is not phototoxic.

Cardiovascular safety evaluation of darolutamide investigated within the frame of systemic toxicity studies in dogs, did not reveal any significant cardiovascular effects up to the highest dose levels tested after oral dosing. The mean maximum concentrations (C_{max}) of darolutamide in dog plasma at the highest dose levels in the 28–day, 13–week and 39–week toxicity studies were 9,990, 6,030 to 8,350 and 12070–12440 ng/mL, respectively.

In an anesthetized dog model using bolus IV administration, darolutamide and its main human diastereomer (*S*,*S*)-darolutamide, at observed mean C_{max} values of >9,300 ng/mL and >4,000 mg/mL in plasma, respectively, induced vasodilatation, especially at the peripheral level, leading to decreased arterial blood pressure (BP). This is not regarded to be of biological relevance as this was observed at free peak plasma concentrations of ≥3–fold higher than the plasma free peak concentrations observed at 700 mg bid dose level in the Phase I/II clinical study in mCRPC subjects.

In the study with (*S*,*S*)-darolutamide, 1 dog out of 4 displayed a reversible complete atrioventricular (AV) block at the highest bolus dose. At this dose, the mean C_{max} of (*S*,*S*)-darolutamide in dog plasma was 27,200 ng/mL, indicating that (*S*,*S*)-darolutamide may affect AV conduction at very high systemic exposure levels. The mechanism and etiology of vasodilatation and AV block are not known, but they might be multifactorial and at least partly related to a synergistic effect of the anesthetic agents used and secondary pharmacodynamic (PD) effects of darolutamide and its main human diastereomer (*S*,*S*)-darolutamide. Based on *in vitro* human ether-a-go–go– related gene and calcium channel inhibition and *in vivo* dog studies, the risk for QT interval prolongation appears low.

Functional *in vitro* studies evaluating secondary PD effects showed that darolutamide inhibits 5-hydroxytryptamine (5–HT) uptake and type–A γ–aminobutyric acid ($GABA_A$) receptors. However, due to the low brain/plasma ratio, central nervous system (CNS) effects via 5–HT uptake and $GABA_A$ inhibition are not expected. *In vivo* safety pharmacology evaluations confirmed that darolutamide has no remarkable effects on CNS or respiratory function. At high local doses/concentrations in the gastrointestinal (GI) tract, darolutamide may affect gastric emptying and intestinal transit.

3.2.4 Drug–drug interactions

The information on darolutamide drug-drug interactions is provided in the latest available version of the Investigator's Brochure (IB) for darolutamide.

Docetaxel will be administered after randomization according to standard treatment practice. Docetaxel is mainly metabolized by CYP3A4. Thus, inducers or inhibitors of CYP3A4 may alter the PK of docetaxel. Darolutamide has no inhibitory but may have some inducing effect on CYP3A4 substrates. Docetaxel is also a substrate of P–gp and OATP1B3. An effect of darolutamide on the PK of docetaxel could, therefore, not be excluded. The potential impact of darolutamide on docetaxel PK, and the respective impact on safety was investigated on the day of the first docetaxel administration in the first 20 subjects who were randomized and

have received at least 1 cycle of docetaxel. The data did not reveal any significant impact of darolutamide on the PK of docetaxel.

3.2.5 Clinical studies with darolutamide

As of 02 OCT 2015, 173 subjects with mCRPC have been treated with darolutamide.

Darolutamide has been studied in 7 clinical trials: a first–in–man study with cohort expansion (Study 17829 / 3104001, ARADES), a long–term safety extension study for the first–in–man study (Study 18035 / 3104002, ARADES–EXT), and a bioavailability study (Study 17830 / 3104003, ARAFOR). Additionally, there is a phase III efficacy and safety study of darolutamide in men with high risk non–metastatic ongoing CRPC (Study 17712 / 3104007, ARAMIS), a Phase I mass balance and bioavailability study in healthy male subjects (Study 17831 / 3104005, ARIADME), a phase I study in Japanese subjects with mCRPC (Study 17719) and a phase I drug–drug interaction study in healthy male and female subjects (Study 17723).

Darolutamide treatment has been well tolerated up to the highest pre–specified dose of 900 mg bid. The maximum tolerated dose was not reached, and no dose–limiting toxicities were observed in the phase I dose–escalation. Escalation of doses in the phase I study was discontinued because a plateau in bioavailability of darolutamide was observed.

Following oral administration of darolutamide at doses of 100, 200, 300, 500, 700, and 900 mg bid, both diastereomers, (*S,R*)-darolutamide and (*S*,*S*)-darolutamide, were slowly absorbed after administration with a light breakfast, the median t_{max} was 2–5 h.

AUC and C_{max} of darolutamide, (*S,R*)-darolutamide, and (*S*,*S*)-darolutamide increased in a nearly dose–proportional manner at doses 100–700 mg bid. At the 900 mg bid dose level, there was no further increase of C_{max} or AUC observed compared to 700 mg dose bid. The concentration of the active metabolite keto-darolutamide was 1.6–2.4 times higher than of the parent compound darolutamide. This ratio was dose–independent. After repeated oral administration of darolutamide, steady–state conditions seemed to be reached after 7 days at the latest. The diastereomer ratio of (*S,R*)-darolutamide to (*S*,*S*)-darolutamide was about 1:6 under steady–state conditions. The terminal half–life of darolutamide was in the range of 11.5–16.1 hours after single oral administration of a tablet formulation.

A food effect was observed when darolutamide was administered after a standardized high-fat, high–calorie breakfast. The exposure and C_{max} were about 50% lower when darolutamide was administered under fasting conditions.

Considering the 164 mCRPC patients as of 02 OCT 2015 treated with darolutamide in the Studies 17829 / 3104001, ARADES, 17830 / 3104003, ARAFOR, and 18035 / 3104002, ARADES–EXT, the integrated safety data showed 93.3% of subjects developed at least 1 adverse event (AE) and Grade 3 or higher AEs were reported in 28% of subjects. The most common AEs have been fatigue in 26.8% of subjects, back pain (22%). The most common AEs considered related to study treatment by the Investigator have been fatigue (9.8%) and hot flush (4.3%). The majority of AEs (91%) were classified as Grade 1 to 2. No dose–related trends were noted for the occurrence of any AEs.

Forty–five subjects (27.4%) have experienced a total of 125 serious adverse events (SAEs) from the start of study treatment and 7 subjects (4%) have died. None of these events was considered related to the study treatment by the Investigator or by the Sponsor.

Eleven subjects (6.7%) have withdrawn from the studies due to an AE. Only 1 of these AEs (fatigue, Grade 2) was considered related to the study treatment by the Investigator.

No events of seizure have been reported during darolutamide treatment period.

Seven patients (7/164) experienced falls or accidental falls. Two out of those seven patients who had a fall or accidental fall experienced SAEs. All SAEs were resolved/improved after treatment. Nine patients (9/164) experienced non–pathological fractures. Four patients experienced SAEs. All serious events of fractures were secondary to a fall, an accidental wound, or syncope. Among the other five patients who experienced non–serious fractures, only one patient had a fall. None of those events were assessed as related to darolutamide or resulted in permanent discontinuation from the study due to the events.

No safety concerns were raised from the ongoing Studies. In Japanese Phase I study, one SAE of grade 3 nausea was reported as related to darolutamide by Investigator, however, due to preexisting confounding factors, the sponsor assessed the event as not related with darolutamide treatment.

Efficacy results show that darolutamide has substantial antitumor activity in subjects with metastatic CRPC for time to PSA progression and for 12–week changes from baseline in serum PSA, soft tissue and bone lesions, and circulating tumor cell (CTC) count. Anti–tumor effects were observed at all dose levels. Anti–tumor activity was better in chemotherapy-naïve CYP17i–naïve subjects compared to post–chemotherapy CYP17i–naïve subjects and post-CYP17i subjects. The higher doses seemed to have a better response than the lower doses, particularly in chemotherapy–naïve CYP17i–naïve subjects.

Further details can be found in the latest available version of the IB, which contains comprehensive information on the study drug.

3.3 Rationale of the study

Management of advanced prostate cancer has evolved considerably in recent years and new therapeutic agents with diverse mechanisms of action have dramatically changed the paradigm of treatment. However, the vast majority of advances have been made in subjects with metastatic castration–resistant disease. Fewer advances have been made in the earlier, hormone–responsive stage of metastatic disease.

ADT remains the mainstay of treatment in metastatic hormone–sensitive prostate cancer. However, despite the demonstrated antitumor activity of ADT in mHSPC, subjects ultimately progress and die of CRPC (5; 6; 7).

The variations upon ADT timing and schedule have not resulted in substantial changes in clinical outcome. Similarly, combined androgen blockade using both an LHRH agonist and an anti–androgen has shown a modest survival benefit over castration, with higher toxicity and costs (12; 13; 14).

The treatment scenario of mHSPC has only recently been challenged, when the randomized controlled CHAARTED trial showed improved survival with upfront chemotherapy (docetaxel) combined with ADT compared to standard ADT in men with metastatic hormone–sensitive prostate cancer, with a 17–month median OS benefit in those with high volume disease (25). Recent data from the STAMPEDE trial confirm the role of upfront chemo–hormonal therapy in mHSPC, showing a significant improvement in OS for subjects with metastatic disease treated with docetaxel in addition to ADT (26; 27).

Docetaxel combined with ADT is, therefore, anticipated to become a new standard for subjects with mHSPC.

It is clear that while ADT is the backbone of treatment, and upfront chemotherapy combined with ADT considerably improves survival, hormone–sensitive disease remains an area of active investigations. Novel treatment approaches are needed to improve disease control and survival and delay castration resistance.

Darolutamide is a novel non–steroidal AR inhibitor lacking a significant agonist action on AR, unlike first generation anti–androgens. It has high binding affinity to AR and a distinctive ability to decrease testosterone–mediated nuclear localization of AR in AR overexpressing cells. In phase I–II clinical studies, darolutamide has demonstrated a very favorable safety profile, with no dose–limiting toxicities observed, and substantial antitumor activity in mCRPC, with effect on both serum PSA and soft tissue and bone lesions. A phase III trial is ongoing to compare darolutamide versus placebo in men with non–metastatic CRPC.

The excellent tolerability and the clinical activity demonstrated so far in phase I/II in mCRPC provide the rationale to explore the efficacy of darolutamide in the earlier stages of metastatic hormone–sensitive prostate cancer, where novel therapeutic strategies are needed to improve the outcome of subjects before castration resistance occurs.

This randomized phase III study aims to demonstrate that the addition of darolutamide to ADT and docetaxel chemotherapy significantly prolongs OS over placebo in mHSPC subjects.

Based on *in vitro* transporter inhibition and *in vitro* CYP3A4 induction results with darolutamide, a small effect on docetaxel exposure during concomitant treatment with darolutamide cannot be excluded. It is, therefore, planned to investigate the potential impact of darolutamide on docetaxel PK and the respective impact on safety on the day of the first docetaxel administration in the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel (see Section 13.1.1). Based on the mechanisms described above as well as known safety profiles from darolutamide and docetaxel, the toxicities from the

combination therapy are expected to be well managed. Therefore, the study will continue subject accrual during this PK and safety review period.

3.4 Benefit–risk assessment

Darolutamide treatment has been well tolerated in clinical studies in mCRPC subjects. There is no important risk identified. Fall and non–pathological fractures are currently considered important potential risks. No dose–limiting toxicities were observed in the phase I dose escalation. The AE profile observed reflects a profile that is expected in a population of subjects with advanced prostate cancer. Most AEs were Grade 1 to 2 and assessed by the investigators as not related to the study treatment. No dose–related trends were noted in the AE profile. Antitumor activity was seen at all dose levels as evaluated by PSA, CTC counts, and soft and bone lesion imaging. Subjects who were naïve to treatment with chemotherapy or CYP17i have responded best to darolutamide treatment.

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

As presented in the previous section, ADT and docetaxel have demonstrated significant survival benefits with the tolerable toxicities and is anticipated to become a new standard for subjects with mHSPC.

Overall, the benefit/risk assessment for darolutamide in addition to standard ADT and docetaxel therapy for mHSPC subjects is positive.

4. Study objectives

The primary objective of this study is:

- To demonstrate the superiority in OS of darolutamide in addition to standard ADT and docetaxel over placebo in addition to standard ADT and docetaxel

The secondary objectives of this study are to evaluate:

- Time to castration–resistant prostate cancer
- Time to initiation of subsequent antineoplastic therapy
- Symptomatic skeletal event free survival (SSE–FS)
- Time to first symptomatic skeletal event (SSE)
- Time to initiation of opioid use for ≥7 consecutive days
- Time to pain progression
- Time to worsening of physical symptoms of disease based on NCCN–FACT FPSI–17
- Safety

The exploratory objectives of this study include:

- Quality of life
- Medical resource use
- Prostate–specific antigen (PSA) assessments
- Pharmacokinetics and exposure–response analysis
- Evaluate biomarkers to investigate the drug (i.e. mode–of–action–related effect and / or safety) and / or the pathomechanism of the disease

5. Study design

Design overview

This is an international, randomized, double–blind, placebo–controlled phase III study of darolutamide in subjects with mHSPC.

The estimated sample size is approximately 1,300 subjects (see Section 10.4).

The start of the study period is defined by signing of the informed consent form (ICF). After an up to 28–day Screening period, subjects meeting the eligibility criteria (i.e. all of the inclusion criteria and none of the exclusion criteria [see Sections 6.1 and 6.2]) will be randomly assigned in a 1:1 ratio to treatment with one of the study drugs (darolutamide or placebo):

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

All subjects must receive ADT of Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, started ≤12 weeks before randomization. For subjects receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 4 weeks prior to randomization is recommended.

Six cycles of docetaxel will be administered after randomization.

Docetaxel can be administered in combination with prednisone/prednisolone at the discretion of the Investigator.

For the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, and for whom a detailed mandatory PK analysis will be performed, docetaxel should be administered at least 14 days after randomization (i.e. start of study drug).

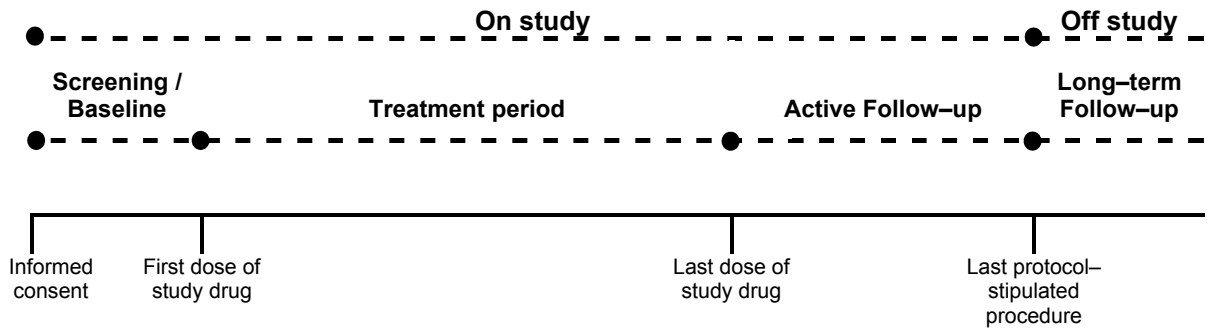
Subjects will be stratified at randomization as follows:

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

Note: Blood samples to measure ALP levels for stratification will be analyzed in a central laboratory.

A schematic of the study periods is presented in Figure 5–1.

Figure 5–1 Study periods schematic



The study will comprise 4 consecutive periods: Screening, Treatment, Active Follow–up, and Long–term (survival) Follow–up.

Screening period:

All trial–related procedures and evaluations will only be performed after the subject has agreed to participate and has signed the ICF. The Screening period will consist of multiple evaluations that will take place within 28 days prior to randomization to ensure that all eligibility criteria are met.

Once eligibility is confirmed and documented, eligible subjects will be randomized in a ratio of 1:1 to treatment with darolutamide or placebo.

Treatment period:

The start of the treatment period is defined by the first administration of study drug. Treatment will be provided for all subjects twice daily until disease progression (symptomatic progressive disease, change of antineoplastic therapy), unacceptable toxicity, consent withdrawal or withdrawal from the study at the discretion of the Investigator or his/her designated associate(s), death, or non–compliance.

Subjects will be evaluated every 12 weeks for CRPC, initiation of subsequent antineoplastic therapy, SSEs, opioid use for ≥7 consecutive days, pain progression, worsening of physical symptoms of disease based on NCCN–FACT FPSI–17, AEs and SAEs, QoL and PSA assessment.

Active Follow–up period:

The Active Follow–up period is the interval from the end–of–study drug intake to the end of all protocol–specified post–treatment interventions.

It includes:

- End of Treatment Visit (EOT)

An EOT Visit will be conducted 30 (+7) days after the last dose of study drug. The following assessment will be performed: QoL, pain assessment, analgesic consumption, subsequent antineoplastic treatments for prostate cancer, which should be provided with start and stop dates and reason for change (PSA progression, clinical progression, radiological progression, toxicity, other), SSEs, and all AEs and SAEs regardless of causality.

- Active Follow–up visits

During the Active Follow–up period, the following assessment will be performed during standard of care clinic visits approximately every 12 weeks for up to 1 year: QoL, pain assessment, analgesic consumption, survival status, subsequent antineoplastic treatments for prostate cancer, which should be provided with start and stop dates and reason for change (PSA progression, clinical progression, radiological progression, toxicity, other), SSEs, and study drug–related SAEs with concomitant medications received. After approximately 1 year of Active Follow–up, subjects will be transitioned to Long–term (survival) Follow–up. The Active Follow–up period extends from the discontinuation of treatment period for up to 1 year or until the subject can no longer travel to the clinic, dies, is lost to follow–up, or withdraws informed consent and actively objects to collection of further data.

Long–term Follow–up period:

After Active Follow–up, subjects will continue to be contacted approximately every 12 weeks (by phone) to capture all antineoplastic treatments for prostate cancer with start and stop date and reasons for change (PSA progression, clinical progression, radiological progression, toxicity, other), study drug–related SAEs with concomitant medications received, and survival status. The end of Long–term Follow–up period is death, lost to follow–up, consent withdrawal, or end–of–study.

Survival sweep:

For every formal analysis of OS, survival data will be collected through additional survival sweeps. All subjects considered alive at the database cut-off date and prior to any subsequent additional analysis will be contacted for survival status.

End–of–study

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (European Union [EU] and non–EU).

This study will end when all subjects on darolutamide treatment have transitioned into a separate program to continue receiving darolutamide (see Section 8.2) or have discontinued the study for any other reason (e.g. death, lost to follow-up, consent withdrawal with no further data collection), and all subjects on placebo have discontinued treatment.

Until transition to the separate program, subjects on darolutamide treatment will continue to follow all the protocol required procedures and visits in the current protocol. Once the separate program is available for subjects to move to, study treatment in the current study will no longer be available.

Primary completion

The first analysis of OS will be performed as an interim futility analysis when approximately 153 deaths have occurred. In case the study continues after the futility analysis, a final efficacy analysis of OS will be performed when approximately 509 deaths have occurred and will be considered the primary completion. The database cut–off date for this analysis will be the date of primary completion.

6. Study population

6.1 Inclusion criteria

Subjects must meet the following criteria at the time of Screening:

1. Written informed consent.
2. Males ≥18 years of age.
3. Histologically or cytologically confirmed adenocarcinoma of prostate.
4. Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, either by contrast–enhanced abdominal/pelvic/chest computed tomography (CT) or magnetic resonance imaging (MRI) scan assessed by Investigator and confirmed by central radiology review. Metastatic disease is defined as either malignant lesions in bone scan or measurable lymph nodes above the aortic bifurcation or soft tissue/visceral lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (31). Lymph nodes are measurable if the short axis diameter is ≥15 mm, soft tissue/visceral lesions are measurable if the long axis diameter is ≥10 mm.
   - Subjects with regional lymph node metastases only (N1, below the aortic bifurcation) will not be eligible for the study. Only subjects with non–regional lymph node metastases (M1a) and/or bone metastases (M1b) and/or other sites of metastases with or without bone disease (M1c) will be eligible.
5. Subjects must be candidates for ADT and docetaxel therapy, per Investigator's judgment.
6. Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first generation anti–androgen, but no longer than 12 weeks before randomization. For subjects receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 4 weeks prior to randomization is recommended. First generation anti–androgen has to be stopped prior to randomization.
7. An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
8. Blood counts at Screening: hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥1.5x10^9/L, platelet count ≥100x10^9/L (subject must not have received any growth factor within 4 weeks or a blood transfusion within 7 days of the hematology laboratory sample obtained at Screening).
9. Screening values of serum alanine aminotransferase (ALT) and/or aspartate transaminase (AST) ≤1.5 x ULN, total bilirubin ≤ULN, creatinine ≤2.0 x ULN.

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

6.2 Exclusion criteria

Subjects who meet any of the following criteria at the time of Screening will be excluded:

1. Prior treatment with:
   - LHRH agonist/antagonists started more than 12 weeks before randomization
   - Second–generation AR inhibitors such as enzalutamide, ARN–509, darolutamide, other investigational AR inhibitors
   - CYP17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as antineoplastic treatment for prostate cancer
   - Chemotherapy or immunotherapy for prostate cancer prior to randomization
2. Treatment with radiotherapy (external beam radiation therapy [EBRT], brachytherapy, or radiopharmaceuticals) within 2 weeks before randomization.
3. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation of the study drugs.
4. Contraindication to both CT and MRI contrast agent.
5. Had any of the following within 6 months before randomization: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure (New York Heart Association Class III or IV).
6. Uncontrolled hypertension as indicated by a resting systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite medical management.
7. Had a prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e., pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥5 years before randomization and from which the subject has been disease-free.
8. A GI disorder or procedure which is expected to interfere significantly with absorption of study drug.
9. An active viral hepatitis, known human immunodeficiency virus infection with detectable viral load, or chronic liver disease with a need of treatment.
10. Previous (within 28 days before the start of study drug or 5 half–lives of the investigational treatment of the previous study, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s).

11. Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the subject and/or his/her compliance with study procedures, or may interfere with the subject's participation in the study or evaluation of the study results.
12. Inability to swallow oral medications.
13. Close affiliation with the investigational site (e.g., a close relative of the Investigator, dependent person [e.g., employee or student of the investigational site]).
14. Previous assignment to treatment in this study.

For prohibited concomitant therapy, please refer to Section 8.1.3.

6.3 Justification of selection criteria

The inclusion/exclusion criteria used in this study, including concomitant conditions and medications as outlined above and in Section 8.1 are based upon knowledge of the known toxicity profile of the agent under investigation and the understanding of the concomitant conditions associated with prostate cancer. To ensure that subjects are in the earliest stages of mHSPC, before castration resistance occurs, ADT initiation within 12 weeks before randomization was selected as an inclusion criterion.

The selection criteria were chosen to ensure, to the best of the Sponsor's ability, the safety of the subjects who may participate in this study.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

General procedures

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records.

The subject may object to the generation and processing of post–withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

Withdrawal from the treatment with study drug

Subjects must be withdrawn from the treatment with study drug if any of the following occurs:

- If, in the Investigator's opinion, continuation of the study drug would be harmful to the subject's well–being
- Disease progression (symptomatic progressive disease, change of antineoplastic therapy)
- Unacceptable toxicity
- Any subject requiring study drug interruption >28 consecutive days
- Any subject requiring dosing of the study drug below 300 mg bid
- Occurrence of Grade 3 or higher treatment–related AE while the subject is on 300 mg bid

Note: Study drug discontinuation (i.e., discontinuation during the treatment period) does not constitute withdrawal from the study. Every effort should be made to retain subjects who discontinue the treatment period for any reason. These subjects are to be encouraged to remain on the study for follow–up of primary, secondary, and exploratory endpoints (i.e., continue in the Active Follow–up period or Long–term Follow–up period). Subjects are expected to participate in follow–up unless they explicitly object. Withdrawal of consent should be documented in the subject's medical file. For guidance on docetaxel background treatment, see Section 7.4.3.

Withdrawal from study

Subjects must be withdrawn from the study if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- At the specific request of the Sponsor and in liaison with the Investigator (e.g. obvious non–compliance, safety concerns)
- Sponsor terminates the study

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure". The reason will be documented in the source documentation and the electronic case report form (eCRF) and the subject will discontinue participation in study with no further follow–up required.

Re–screening of a subject who did not fulfill the eligibility criteria is allowed within 2 weeks from the prior screen failure date. If a subject is re–screened, a new screening number will be allocated and a link will be made between the screening numbers of the same subject.

Re–screening of screen failed subjects may only be allowed once after discussion with the Bayer–designated medical representative or Sponsor and after approval by the Sponsor. Sponsor approval of re–screening for a screen failed subject must be documented.

The subjects who need to repeat the screening procedures will be re–consented.

In any case, the Investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk.

Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been randomized.

6.4.2 Replacement

A subject withdrawn from the treatment with study drug will not be replaced.

6.5 Subject identification

The subject number is a 9–digit number consisting of:

Digits 1 to 2 = Country code

Digits 3 to 5 = Center number within the country

(Digits 1 to 5 = Trial unit)

Digits 6 to 9 = Current subject number within the center

7. Treatment(s)

7.1 Treatments to be administered

Study drugs

The following treatment groups are defined for this study:

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

Background treatment

All subjects must receive ADT of Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy.

Six cycles of docetaxel will be administered after randomization. Docetaxel can be administered in combination with prednisone/prednisolone at the discretion of the Investigator. The first cycle of docetaxel should be administered within 6 weeks after start of study drug. For the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, and for whom a detailed mandatory PK analysis will be performed, docetaxel should be administered at least 14 days after randomization (i.e. start of study drug). Docetaxel should be prepared at the study centers in accordance with the product information and/or local standards and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy following within one hour after the administration of study drug. Administration of study drug in these 20 subjects should come before docetaxel administration.

7.2 Identity of study treatment

7.2.1 Darolutamide and placebo

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the Sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the Sponsor's clinical supplies Quality Assurance group.

A complete record of batch numbers and expiry dates of all study drugs as well as the labels will be maintained in the Sponsor's study file.

Darolutamide and matching placebo tablets will be provided by Bayer AG.
The items in Table 7–1 describe the elements used to identify each study drug.

Table 7–1 Study drug identifiers

Name	Darolutamide	Placebo
Formulation	Film coated tablets for oral administration	Film coated tablets for oral administration
Appearance	Blue oval shaped tablets embossed with 'OR–300'	Blue oval shaped tablets embossed with 'OR–300'
Galencial form	Film coated tablet	Film coated tablet
Composition	Drug substance: 300 mg BAY1841788 Excipients: Lactose monohydrate Calcium hydrogen phosphate anhydrous Croscarmellose sodium Povidone Magnesium stearate Laquer blue	Excipients: Lactose monohydrate Cellulose microcrystalline Calcium hydrogen phosphate anhydrous Croscarmellose sodium Povidone Magnesium stearate Laquer blue
Strength	300 mg	Not applicable
Bayer number	BAY 1841788	Not applicable
Packaging	White plastic bottles of HDPE each containing 140 tablets	White plastic bottles of HDPE each containing 140 tablets

Abbreviations: HDPE = high density polyethylene.

7.2.2 Background docetaxel treatment

Docetaxel is commercially available. The participating investigators are required to consult the product information for docetaxel.

All treatment provided by the Sponsor will be labeled according to the requirements of local law and legislation. Label text will be approved according to the Sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request. For all study treatment provided by the Sponsor, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study treatment can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the Sponsor's clinical supplies Quality Assurance group. A complete record of batch numbers and expiry dates as well as the labels of all study treatments provided by the Sponsor will be maintained in the Sponsor study file.

7.3 Treatment assignment

At the end of the screening period, all subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomly assigned on a 1:1 basis in a blinded fashion to treatment with darolutamide or matching placebo plus ADT and docetaxel. In addition, randomization will be stratified by:

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

Note: Blood samples to measure ALP levels for stratification will be analyzed in a central laboratory.

A computer–generated randomization list will be prepared by the Bayer Randomization Manager. The randomization number will be used to link the subject to a treatment group and to a medication package.

The Investigator (or designated associate) will obtain the randomization number and the medication package numbers assigned to a subject by accessing the Interactive Voice/Web Response System (IXRS) after confirming that the subject meets all the inclusion criteria and does not meet any of the exclusion criteria.

An IXRS description and handbook will be provided to each investigational site.

7.4 Dosage and administration of study treatment

7.4.1 Dose modifications of study drug

The study drug will be administered as oral 300 mg tablets. The dose of study drug to be administered is 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg. Placebo matching darolutamide tablets in appearance will be administered twice daily with food.

The dose or dosing schedule of the study drug may be modified following the occurrence of clinically significant AEs. Doses of study drug may be delayed or reduced in case of clinically significant toxicities that are considered by the Investigator to be related to study drug. Toxicities will be graded using the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI–CTCAE) v 4.03. All dose modifications regardless of relatedness should be recorded on the eCRF. If a subject experiences several study drug–related toxicities with different grading, the recommendation of the worst grading should be used.

If a dose of study drug is delayed, dose can be taken up to 6 hours later with food to make up for the missed one.

7.4.1.1 Dose interruption

The maximum time for a dose interruption period is 28 consecutive days. Any subject requiring treatment interruption >28 consecutive days must be withdrawn from treatment with study drug.

7.4.1.2 Dose reduction

If considered necessary for subject's safety, the dose of study drug may be reduced to 300 mg bid. The medical monitor must be notified of any darolutamide dose reduction.

Dosing of the study drug below 300 mg bid is not allowed. If a Grade 3 or higher treatment-related AE occurs while the subject is on 300 mg bid, the subject must be withdrawn from the treatment with study drug.

7.4.1.3 General recommendations for dose modifications of study drug

A subject who experiences a treatment–related Grade 3 or 4 AE should interrupt study drug until the AE improves to Grade 2 or less. Treatment with study drug is then to be restarted at 300 mg bid.

Additional details are provided in Table 7–2.

Table 7–2 Study drug dose modifications

Severity grade (NCI–CTCAE v 4.03)	Dose modifications	Study treatment withdrawal
Grade 0–2	Treat on time. Per Investigator's decision to interrupt or reduce study drug [a,b]	—
Grade 3 or 4	Delay until ≤ Grade 2 [a] When the severity is Grade ≤2, restart at a reduced dose of 300 mg bid [b,c]	If the dosing of the study drug is temporally or permanently reduced to 300 mg bid and a Grade 3 or higher treatment–related AE occurs while the subject is on a dose of 300 mg bid, the subject must be withdrawn from treatment with study drug

Excludes clinically nonsignificant and asymptomatic laboratory abnormalities.
Abbreviations: AE = adverse event; bid = twice daily; NCI–CTCAE v 4.03 = National Cancer Institute–Common Terminology Criteria for Adverse Events version 4.03.
[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, dose escalation to 600 mg bid may be considered at the discretion of the Investigator.
[c] If, following a dose reduction, dose is escalated to 600 mg bid and a second treatment–related AE with a severity of Grade 3 or higher occurs, a permanent dose reduction to 300 mg bid is required. A third occurrence of a Grade 3 or higher treatment–related AE requires permanent discontinuation of treatment with study drug.

7.4.2 Dosage and administration for background treatment

All subjects must receive ADT of Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy.

The docetaxel dose to be administered is 75 mg/m^2 Day 1 as 1 hour IV infusion every 21 days, in line with the summary of products characteristics. At Investigator's discretion, longer infusions are allowed for medical reasons. The cycle should be repeated every 3 weeks for 6 cycles. Docetaxel can be administered in combination with prednisone/prednisolone at the discretion of the Investigator. To prevent hypersensitivity reactions and fluid retention, the recommended pre–medication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. Anti-emetic regimens are recommended as per local clinical practice.

7.4.3 Dose modifications of docetaxel background treatment

Dose adjustments of docetaxel should be made based on the specific types of toxicities observed, graded using NCI–CTCAE v4.03.

Docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all subjects receiving docetaxel.

Docetaxel should not be given to subjects with bilirubin >ULN, or to subjects with AST and/or ALT >1.5 x ULN. Bilirubin, AST and ALT values should be obtained prior to each cycle of docetaxel. In subjects who experienced either febrile neutropenia, neutrophil count <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 75 to 60 mg/m^2. If the subject continues to experience these reactions at 60 mg/m^2, the docetaxel treatment should be discontinued. Should treatment with docetaxel be discontinued for any reason before completion of 6 cycles, the treatment with study drug may be continued.

7.5 Blinding

Subjects will be randomized to receive darolutamide or matching placebo in a double–blind fashion such that neither the Investigator, nor the Sponsor, nor the subject will know which agent is being administered. The randomization number will be assigned through the IXRS based on information supplied by the Investigator at the time of randomization.

Darolutamide and placebo will be identical in appearance in order to preserve blinding. To maintain the blind, study drugs (either darolutamide or matching placebo) will be packaged in a drug pack labeled with a unique drug pack number. The study drug pack number will be assigned to the subject through the IXRS.

The DMC will review in an unblinded manner the safety data and PK of the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel. However, the investigators, subjects and the Sponsor will remain blinded.

Bioanalytic analysis of darolutamide and docetaxel PK samples will be performed by an unblinded bioanalyst at an external laboratory.

SUSAR unblinding

In the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see Section 9.6.1.4) related to the blinded treatment, the subject's treatment code will usually be broken before reporting to health authorities and central ethics committees in an unblinded fashion. In compliance with the European Commission's Detailed Guidance on the collection and verification of presentation of AE/reaction reports arising from clinical trials on medicinal products for human use, investigators and persons responsible for the ongoing conduct of the study will not usually receive unblinded copies of SUSAR reports, unless unblinded information is judged necessary for safety reasons.

Emergency unblinding by the Investigator

Investigators may only unblind subjects under emergency unblinding rules. If a subject is unblinded by the Investigator, they must discontinue study drugs.

Investigators should note that emergency unblinding is reserved for emergency situations where lack of knowledge about the actual study drug treatment interferes with appropriate emergency management.

The occurrence of an SAE should not routinely precipitate the immediate unblinding of the label. Progressive disease itself does not routinely constitute an emergency situation, therefore unblinding the label only for subsequent treatment decision is not allowed.

If emergency unblinding is necessary for the treatment of a subject for an SAE, the treatment with study drug can be unblinded via the IXRS system (refer to the IXRS manual for instructions). The participating site has unrestricted and immediate access to break the treatment code in IXRS. Should the blinded code be broken for a subject, the medical monitor or designee should be contacted by the principal investigator (PI) within 1 working day of unblinding to discuss the rationale for the premature unblinding.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the Sponsor (or its affiliate/contract research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file; the site–relevant elements of this information will be available in the Investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IXRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the Sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

The Investigator or designated associate(s) are responsible for dispensing the study drugs (darolutamide or placebo).

The Investigator is responsible for control of the distribution and use of the study drug. Bottles must be returned to the Investigator with all unused medication. Throughout the study, all unused study drug must be accounted for. This information will be recorded in the drug dispensing log.

Study subjects should be instructed to return all unused tablets to the study site at their next study visit for drug accountability and proper disposal. Study subjects must be instructed not to dispose of unused tablets on their own. Drug accountability should be done at the time bottles are returned by the subject. Any discrepancies should be reported immediately upon discovery.

7.7 Treatment compliance

Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records.

8. Non–study therapy

8.1 Prior and concomitant therapy

All subjects must receive an ADT of the Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy started ≤12 weeks before randomization (if combined with a first–generation anti–androgen, such as bicalutamide, flutamide, nilutamide, or cyproterone acetate, it must be stopped before randomization). For subjects receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 4 weeks prior to randomization is recommended.

Six cycles of docetaxel will be administered after randomization.

Docetaxel can be administered in combination with prednisone/prednisolone at the discretion of the Investigator.

8.1.1 Prior therapy

All medications taken in the first 28 days prior to randomization (including start/stop dates, dose frequency, route of administration, and indication) must be recorded in the subject's source documentation, as well as entered in the appropriate pages of the eCRF. Prior local treatment for prostate cancer (surgery and/or radiation) before the time of informed consent (IC) is allowed and should be recorded in the medical record and in the appropriate eCRF. Prior treatment with LHRH agonist/antagonists started more than 12 weeks before randomization, second–generation AR inhibitors, other investigational AR inhibitors, CYP17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as antineoplastic treatment for prostate cancer is not allowed. Prior chemotherapy or immunotherapy for prostate cancer is not allowed. Treatment with radiotherapy (EBRT, brachytherapy, or radiopharmaceuticals) within 2 weeks before randomization is not allowed. Blood transfusions are not allowed within 7 days and growth factors are not allowed within 4 weeks of the hematology laboratory sample obtained at Screening. For a detailed list of prohibited medications and treatments, see Sections 6.2 and 8.1.3.

8.1.2 Permissible concomitant medications and treatments

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

Analgesic use will be captured via eCRF. Physicians are to record which opioid and non–opioid medications were used since the last visit, and physicians are to record exact daily doses of each analgesic consumed in the last 24 hours prior to the visit (Analgesic 24 hour consumption log –eCRF). Note that analgesic medication should be recorded via eCRF for each visit that pain is assessed via the Brief Pain Inventory short form (BPI–SF).

Palliative radiation therapy or surgical intervention as needed are allowed during study treatment. Treatment with biphosphonates and denosumab is allowed.

All subjects must receive ADT of Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy. Switching ADT to an LHRH antagonist is permitted during study treatment.

For docetaxel pre–medication please refer to Section 7.4.2. Supportive care in case of toxicity related to docetaxel including use of biologic response modifiers such as granulocyte colony-stimulating factor or granulocyte–macrophage colony–stimulating factor, should be applied according to standard practice.

Based on results from a drug–drug interaction study (Study 17726), repeated co-administration of strong CYP3A4 inducers (see listing of drugs in Appendix 16.5) with darolutamide is expected to reduce darolutamide plasma concentrations. Therefore, concomitant intake of strong CYP3A4 inducers should be avoided. It is strongly recommended to use alternative treatments. Concomitant short term use is allowed.

Administration of 600 mg darolutamide bid over 4 days prior to administration of a single dose of 5 mg rosuvastatin, a BCRP, OATP1B1 and OATP1B3 substrate, together with food resulted in a 5.2–fold increase in mean exposure [AUC(0–24)] and a 4.9–fold increase in C_{max} of rosuvastatin in Study 17723. This indicates that co–administration of darolutamide can also increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the patients should be closely monitored for signs and symptoms of increased exposure to BCRP, OATP1B1 or OATP1B3 substrates. Dose modification of these substrates should be considered based on the prescriber information or such compounds should be avoided.

8.1.3 Prohibited concomitant medications and treatments

Concomitant treatment with another systemic antineoplastic therapy or another investigational medicinal product is prohibited with the exception of ADT throughout the study and 6 cycles of docetaxel after randomization.

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

- Any investigational medicinal product
- Radiopharmaceuticals
- Immunotherapy (e.g. sipuleucel–T)
- Cytotoxic chemotherapy other than docetaxel for 6 cycles after randomization
- Enzalutamide, ARN–509, bicalutamide, flutamide, nilutamide
- Abiraterone acetate, TAK–700, or other CYP17 inhibitors
- Systemic ketoconazole as antineoplastic treatment for prostate cancer
- ADT switch to LHRH agonist
- Another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study drug

For prohibited prior therapy, please refer to Section 6.2.

8.2 Post–study therapy

After treatment discontinuation, subjects will enter the Active Follow–up period and then the Long–term (Survival) Follow–up period. Therapy after discontinuation of study treatment will be collected as follows:

During Active Follow–up (includes EOT Visit and Active Follow–up visits):

- EOT Visit: collection of medications related to pain and QoL, and collection of medications for study drug–related SAEs.
- Active Follow–up Visit: collection of all subsequent antineoplastic treatments for prostate cancer (which should be provided with start and stop dates and reason for change PSA progression, clinical progression, radiological progression, toxicity, or other); collection of medications related to pain and QoL, and collection of medications for study drug–related SAEs.

During Long–term (Survival) Follow–up period:

- Long–term Follow–up visits: collection of subsequent antineoplastic treatments for prostate cancer which should be provided with start and stop dates and reason for change (PSA progression, clinical progression, radiological progression, toxicity, or other), and collection of medications for study drug–related SAEs.

After primary analysis of the study:

- For subjects who are ongoing with darolutamide treatment, the sponsor will continue to provide darolutamide via a separate program at least until darolutamide is approved and reimbursed in a specific country.
- Subjects receiving placebo will discontinue the treatment and complete the study. Further treatment is at the discretion of the Investigator.
- Subjects in the Active or Long-term follow-up will complete the study.

9. Procedures and variables

9.1 Tabular schedule of evaluations

All procedures, including efficacy and safety measurements obtained during the course of the study, are summarized in the schedule of assessments (Table 9–1).

Table 9–1 Schedule of assessments

Procedures	Screening Period		Treatment Period[a]		Follow–up Period		
					Active Follow–up Period		Long–term Follow–up Period
			Visit 1	Visit 2 and subsequent visits	EOT Visit	Active Follow–up Visits	
	Within 28 days before randomization	Within 7 days before randomization	Day 1 (+3 days)	Week 12 (±7 days) and every 12 weeks	30 days (+7 days)[u] after last dose of study drug	Approximately every 12 weeks from discontinuation of treatment up to 1 year	Approximately every 12 weeks after Active Follow–up, until death, lost to follow–up, consent withdrawal, or end–of–study
Informed consent	X						
Pharmacogenetic consent (whole blood only)	X						
Demography	X						
Medical history	X						
Prostate cancer history[b]	X						
Eligibility criteria	X	X					
Medical resource use			X	X	X	X	
Symptom/QoL questionnaire NCCN–FACT–FPSI–17[c]		X	X[d]	X	X	X	
Pain questionnaire BPI–SF [c,e]		X	X[d]	X	X	X	
Analgesic 24 hour consumption log – eCRF (physician recording analgesic pain meds consumed over last 24 hours)[c,e]		X	X[d]	X	X	X	
Randomization			X[s]				
Physical examination including weight and height[f]	X		X[g]	X	X		
12–lead ECG		X	X[g]	X	X		
Vital signs (BP, HR)		X	X[g]	X	X		
Laboratory safety assessments (hematology, general chemistry and urinalysis)[h]		X		X	X		

Procedures	Screening Period		Treatment Period[a]		Follow–up Period		
					Active Follow–up Period		Long–term Follow–up Period
			Visit 1	Visit 2 and subsequent visits	EOT Visit	Active Follow–up Visits	
	Within 28 days before randomization	Within 7 days before randomization	Day 1 (+3 days)	Week 12 (±7 days) and every 12 weeks	30 days (+7 days)[u] after last dose of study drug	Approximately every 12 weeks from discontinuation of treatment up to 1 year	Approximately every 12 weeks after Active Follow–up, until death, lost to follow–up, consent withdrawal, or end–of–study
Serum PSA[h]	X			X	X		
Testosterone	X[h]			X[h]	X[h]		
Alkaline Phosphatase for screening[h]	X						
PK samples[i]			X	X			
Plasma collection for genetic biomarkers		X	X	X	X		
Plasma collection for non–genetic biomarkers		X	X	X	X		
Whole blood for CTC analyses			X	X[j]	X		
Whole blood collection for pharmacogenetic analysis – only if pharmacogenetic consent is signed			X	(X)[t]			
Collection of tumor tissue (e.g. biopsy)	X[k]				X[k]		
ECOG PS	X		X	X	X		
CT/MRI [l]	X [m]			(X)[n]			
Bone scan[l]	X [o]			(X)[p]			
First SSE				X	X	X	
SSE–FS				X	X	X	
Post–study antineoplastic therapy[q]						X	X
Survival status[v]						X	X
AEs/SAEs	X	X	X	X	X	X[r]	X[r]
Concomitant treatments	X	X	X	X	X	X[r]	X[r]
Study drug dispensing			X	X			

AE=adverse events, BP=blood pressure, BPI–SF=Brief Pain Inventory – Short Form; CT=computed tomography, CTC=circulating tumor cells, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, eCRF=electronic case report form, HR=heart rate, MRI=magnetic resonance imaging, NCCN–FACT FPSI–17=Functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17–item questionnaire; PK=pharmacokinetics, PSA=prostate–specific antigen, QoL=quality of life, SAE=serious adverse event, SSE=symptomatic skeletal event, SSE–FS=symptomatic skeletal event free survival

[a] Subjects will receive 6 cycles of docetaxel every 21 days after check of the routine hematology and biochemistry blood tests (see Section 9.6.3.1). The first cycle of docetaxel should be administered within 6 weeks after start of study drug. For the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, and for whom a detailed mandatory PK analysis will be performed, docetaxel should be administered at least 14 days after randomization (i.e. start of study drug).

[b] Including treatments and procedures.

[c] Questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

[d] If not collected at the Screening visit.

[e] Analgesic consumption and pain assessment questionnaires must be collected on the same day.

[f] Height to be measured at Screening only.

[g] If not previously done.

[h] PSA and testosterone values are to be assessed by a central laboratory during the study period. In a subset of approximately 300 subjects, additional determination of total and free testosterone will be performed at Screening and repeated every 6 months (Visit 3, Visit 5, etc.), and at the EOT Visit using a liquid chromatography–tandem mass spectrometry method for the analysis of total testosterone. The non–protein–bound (free) testosterone will be analyzed and also calculated with the sex hormone–binding globulin and albumin concentrations, both of which will also be determined. Blood samples to test alkaline phosphatase for stratification purpose will be analyzed in a central laboratory and thereafter by a local laboratory. Other laboratory assessments are to be performed by local laboratories. Specific laboratory assessments are detailed in Section 9.6.3.1.

[i] In the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, several blood samples will be collected on the day of first docetaxel administration, which should be at least 14 days after start of study drug. On this day, blood samples will be collected at the following time points: Pre–Dose (prior to the administration of darolutamide and docetaxel), 20±10 minutes after start of docetaxel infusion, 1 hour (within 5 minutes before the end of the infusion), 90 minutes, 2,3, 4, 6, and 8 hours following the start of docetaxel infusion. For planned time points between 90 minutes and 8 hours, blood samples should be collected within ±15 minutes of the planned time. For all other randomized subjects, 2 blood samples for PK will be collected at least one hour apart on the first day of study drug administration independent of docetaxel administration. The first sample should be taken at least 30 minutes after the first study drug dose. In all randomized subjects, two additional blood samples will be collected at 2 subsequent docetaxel cycles (one sample per docetaxel cycle), at any time relative to study drug administration and after docetaxel administration on the same day. For the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, the first additional blood sample must be taken from docetaxel cycle 2 onwards. Please refer to Section 9.5.1 for further guidance.

[j] To be performed at Visit 2 only.

[k] Collection of tumor tissue at Screening is only if available. Biopsy at disease progression is optional and if available.

[l] Chest, abdomen and pelvic CT or MRI and bone scan should be performed at the end of docetaxel treatment (within 30 days from last cycle of docetaxel) and yearly thereafter.

[m] Contrast–enhanced chest, abdomen, and pelvic CT or MRIs performed within 42 days prior to start of treatment with study drug are acceptable as screening scans if the standard acquisition procedure according to the Imaging Manual was followed.

[n] Chest, abdomen and pelvic CT or MRI can be performed at any time in case of PSA progression, symptomatic progressive disease, or change of antineoplastic therapy or if considered as appropriate in the Investigator's judgment; (X) indicates optional assessment.

[o] Bone scan performed within 42 days prior to start of treatment with study drug are acceptable as screening scan if the standard acquisition procedure according to the Imaging Manual was followed.

[p] Bone scan can be performed at any time in case of PSA progression, symptomatic progressive disease, change of antineoplastic therapy or if considered as appropriate in the Investigator's judgment; (X) indicates optional assessment.

[q] Please note that documentation of post–study antineoplastic therapy must include the start and stop dates of each treatment and reason for treatment changes (PSA progression, clinical progression, radiological progression, toxicity, other).

[r] Only study drug–related SAEs with concomitant medication received.

[s] Randomization must occur within 28 days from ICF signature.

[t] If missed at Visit 1.

[u] For further details, see Section 9.2.3.

[v] For every formal analysis of OS, survival data will be collected through additional survival sweeps. All subjects considered alive at the database cut-off date and prior to any subsequent additional analysis will be contacted for survival status.

9.2 Visit description

Subject study visits are to occur every 12 weeks (±7 days) starting from randomization. The EOT Visit should occur within a minimum of 30 days (+7 days) after last dose of study drug.

The details of these visits are listed in Table 9–1.

9.2.1 Screening period

A prospective study subject will receive both written and verbal information about the study, and will have an opportunity to ask questions and should have sufficient time to decide whether or not to participate in the study. The original signed and dated ICF must be retained in the Investigator's study file and a copy must be provided to the subject.

All subjects for whom the IC procedure is completed successfully will be assigned a subject number.

Subject screening must occur within 28 days prior to randomization. Screening procedures can be performed on separate occasions within the allowed 28 day timeframe. Re–testing is allowed during the 28–day window only if there is a medical or logistical reason. In case screening procedures need to be repeated outside the allowed 28 day timeframe of the screening period, subject should be considered a screen failure. It is estimated that it will take 7 to 14 days to obtain results from the safety laboratory assessments, testosterone, and PSA.

Each subject's eligibility will be confirmed by the Bayer–designated medical representative's written agreement. The Investigator will complete a paper eligibility form confirming the inclusion and exclusion criteria, this will be forwarded to the Bayer–designated medical representative for review and eligibility confirmation which will take into account the results of the central image review for eligibility. The subject will be identified only by their study-specific subject number.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study at any time prior to randomization is regarded a "screening failure".

Please refer to Section 6.4.1 for guidance on re–screening procedures.

The following procedures will be performed during the Screening period:

Within **28** days before randomization:

- Signed and dated ICF
- Informed consent for pharmacogenetic consent (whole blood only)
- Demographic data (date of birth, age, racial group)
- Medical history and current medical condition
- Prostate cancer history including prior treatments and procedures

- Assess eligibility criteria
    - Eligibility must be confirmed by written agreement of the Bayer–designated medical representative
- ECOG PS
- Physical examination including weight and height
- PSA
- Testosterone
    - Note for testosterone: In a subset of approximately 300 subjects, additional determination of total and free testosterone will be performed at Screening and repeated every 6 months (Visit 3, Visit 5, etc.), and at the EOT Visit using a liquid chromatography-tandem mass spectrometry (LC–MS/MS) method for the analysis of total testosterone. The non–protein–bound (free) testosterone will be analyzed and calculated with the sex hormone–binding globulin (SHBG) and albumin concentrations, both of which will also be determined
- Alkaline phosphatase for screening (stratification)
    - Note for alkaline phosphatase test during Screening: blood samples to test alkaline phosphatase for stratification purpose will be analyzed in central laboratory and during treatment period by local laboratory
- Contrast–enhanced chest, abdomen, and pelvic CT or MRI. CT/MRI performed within 42 days prior to start of treatment with study drug are acceptable as screening scans if fulfilling the requirements of the Imaging Manual.

  Radiologic tumor assessments will include, chest, abdomen and pelvis, and will be evaluated locally at the study site and by the central review. The first radiological assessment must be comprised of an IV (and oral, if indicated, per Imaging Manual) contrast enhanced CT/MRI scans of chest, abdomen and pelvis. Scans done up to 42 days prior to first dose can be used as baseline scans fulfilling the requirements in the Imaging Manual. Contrast–enhanced MRI shall be performed instead of CT when local regulations or allergy to CT contrast media do not permit the use of CT as requested per protocol schedule. Copies of scans should be forwarded to the central imaging facility for independent assessment. Subjects with a contraindication to both, CT and MRI contrast agent, should not be enrolled in this study (see exclusion criterion 4).
- Bone scan. Bone scan performed within 42 days prior to start of treatment with study drug is acceptable as screening scan if performed according to the Imaging Manual. Copies of scans should be forwarded to the central imaging facility for independent assessment
- AEs/SAEs and concomitant treatments, including opioid use for pain
- Optional collection of archival tissue – if available– for tissue biomarker analyses unless precluded by local guidelines, e.g. Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) or regulatory authorities

Within **7** days before randomization:

- Functional assessment of cancer therapy/National Comprehensive Cancer Network prostate cancer symptom index (NCCN–FACT FPSI–17) questionnaire (collected via electronic patient reported outcome [ePRO] device)
- Pain questionnaire – BPI–SF (collected via ePRO device)
- Analgesic 24–hour consumption log –eCRF (Physician to record whether or not the subject has initiated opioid therapy since last visit and to record analgesic pain meds consumed by the subject). Should be collected on the same day as pain assessment questionnaires
- A 12–lead ECG
- Vital signs (BP and HR)
- Laboratory safety assessments (hematology, chemistry and urinalysis) (see Section 9.6.3.1)
- A blood (plasma) sample for tumor–related biomarker analysis (genetic and non–genetic) unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities if eligibility has been confirmed (see Section 13)
- AEs/SAEs
- Concomitant treatments, including opioid use for pain
- Confirmation of eligibility

Note: For all visits where questionnaires are administered, the questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

At the end of the screening period, the subject will be randomized.

9.2.2 Study treatment period

9.2.2.1 Day 1 (Visit 1)

Randomization must occur within 28 days from ICF signature. The subject will arrive at the study center on the morning of Day 1 (+3 days). The first dose of study drug will be administered with breakfast at the study center. The following procedures will be performed:

- Medical resource use
- Blood draw for 2 PK samples, which are collected at least 1 hour apart, and the first sample should be taken at least 30 minutes after the first darolutamide dose

In the first 20 subjects who were randomized and have received at least one cycle of docetaxel, detailed mandatory blood sampling for PK analysis of darolutamide, (*S*,*S*)-darolutamide, (*S,R*)-darolutamide, keto-darolutamide, and docetaxel will be collected on the day of the first docetaxel administration which should be at least 14 days after randomization (i.e. start of study drug; see Section 9.5).

- A blood (plasma) sample for tumor–related biomarker analysis (genetic and non-genetic) unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities (see Section 13)
- Whole blood draw for CTC
- Whole blood draw for pharmacogenomics analysis if PI/ICF Pharmacogenetic consent is signed unless precluded by local guidelines, e.g., IEC/IRB or regulatory authorities (see Section 13)
- ECOG PS
- Current medical condition, AEs, SAEs, and concomitant treatments
- Study drug will be dispensed for 12 weeks

If not performed at Screening:

- Functional assessment of cancer therapy/National Comprehensive Cancer Network prostate cancer symptom index (NCCN–FACT– FPSI–17) questionnaire (collected via ePRO device)
- Pain questionnaire – BPI–SF (collected via ePRO device)
- Analgesic 24–hour consumption log –eCRF (Physician to record whether or not the subject has initiated opioid therapy since last visit and to record analgesic pain meds consumed by the subject over last 24 hours). Should be collected on the same day as pain assessment questionnaires
    - To facilitate assessment of analgesic use, subjects should be requested to bring all pain medication consumed to each visit
- Physical examination including weight
- A 12–lead ECG
- Vital signs (BP and HR)

Subjects will continue taking study drug at home throughout the study treatment period.

Note: For all visits where questionnaires are administered, the questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

Note for docetaxel administration: Subjects will receive 6 cycles of docetaxel every 21 days after check of the routine hematology and biochemistry blood tests (see Section 9.6.3.1). The first cycle of docetaxel should be administered within 6 weeks after start of study drug. For the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, and for whom a detailed mandatory PK analysis will be performed, docetaxel should be administered at least 14 days after randomization (i.e. start of study drug).

9.2.2.2 Visit 2 and subsequent visits (every 12 weeks ± 7 days)

The following procedures will be performed:

- Medical resource use
- Symptom / QoL questionnaire NCCN–FACT–FPSI–17

- Pain questionnaire – BPI–SF
- Analgesic 24–hour consumption log –eCRF (Physician to record whether or not the subject has initiated opioid therapy since last visit and to record analgesic pain meds consumed by the subject over last 24 hours). Should be collected on the same day as pain assessment questionnaires
    - To facilitate assessment of analgesic use, subjects should be requested to bring all pain medication consumed to each visit
- Physical examination including weight
- A 12–lead ECG
- Vital signs (BP, HR)
- Laboratory safety assessments (hematology, chemistry and urinalysis) (see Section 9.6.3.1)
- PSA
- Testosterone
    - Note for testosterone: In a subset of approximately 300 subjects, additional determination of total and free testosterone will be performed at Screening and repeated every 6 months (Visit 3, Visit 5, etc.), and at the EOT Visit using a LC–MS/MS method for the analysis of total testosterone. The non–protein–bound (free) testosterone will be analyzed and calculated with the SHBG and albumin concentrations, both of which will also be determined
- At 2 visits, an additional blood draw for PK analysis (see Section 9.5)
- A blood (plasma) sample for tumor–related biomarker analysis (genetic and non–genetic) unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities (see Section 13)
- Collect whole blood sample for CTC (at Visit 2 only)
- ECOG PS
- Chest, abdomen and pelvic CT/MRI: (please refer to Section 9.2.2.3)
- Bone scan: (please refer to Section 9.2.2.3)
- Date of first SSE (if applicable)
- Current medical condition, AEs, SAEs, and concomitant treatments
- Study drug will be dispensed for 12 weeks
- If missed at Visit 1, whole blood collection for pharmacogenetic analysis – only if pharmacogenetic consent is signed

Note: For all visits where questionnaires are administered, the questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

The treatment period will end at each site when all subjects at the site who are ongoing on darolutamide treatment have transitioned into the separate program to continue receiving darolutamide (see Section 8.2) or have discontinued from the study for any other reason (e.g. lost to follow-up, consent withdrawal), and all subjects on placebo have discontinued the treatment.

9.2.2.3 Requirement for chest, abdomen and pelvic CT/MRI and bone scan during the study treatment period

Contrast–enhanced chest, abdomen and pelvic CT or MRI for the assessment of soft tissue/visceral lesions and bone scan for the assessment of bone lesions should be performed at the end of docetaxel treatment (within 30 days from last cycle of docetaxel) and yearly thereafter.

In addition, contrast–enhanced chest, abdomen and pelvic CT or MRI and bone scan can be performed at any time in case of PSA progression, symptomatic progressive disease, change of antineoplastic therapy or if considered as appropriate in the Investigator's judgment. (Section 9.2.5).

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

The method chosen at the baseline should be the same throughout the study. 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.

Radiological progression by soft tissue/visceral lesions is determined according to RECIST criteria, version 1.1 (31), based on MRI / CT scans of the chest, abdomen, and pelvis performed by the Investigator, as recommended by Prostate Cancer Clinical Trials Working Group (PCWG3) (32).

Bone lesions will be recorded separately from soft tissue/visceral lesions. Radiological progression by bone lesions is determined according to PCWG3 criteria based on whole body ^{99m}Tc methylene diphosphonate bone scans performed by the Investigator.

Further guidance for acquisition of images and assessment rules will be provided in the Imaging Manual.

9.2.3 Active Follow–up period

End–of–study treatment visit

Subjects will have an EOT Visit 30 days (+7 days) after the last dose of study drug. Another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study drug.

After primary analysis of the study:

- Subjects in the darolutamide arm, who decide to continue darolutamide treatment in a separate program, will have their EOT Visit for the current study at the same time as their first treatment visit in the separate program.
- Subjects in the darolutamide arm, who then do not decide to continue treatment, will have their EOT visit 30 days (+7 days) after the last dose.
- Subjects in the placebo arm will discontinue treatment and will have their EOT Visit at their earliest convenience, and at the latest 30 days (+7 days) after the last dose.

The following procedures will be performed during the EOT Visit:

- Medical resource use
- Symptom / QoL questionnaire NCCN–FACT–FPSI–17
- Pain questionnaire – BPI–SF
- Analgesic consumption log –eCRF (Physician to record whether or not the subject has initiated opioid therapy since last visit and to record analgesic pain meds consumed by the subject over last 24 hours). Should be collected on the same day as pain assessment questionnaires
- Physical examination including weight
- A 12–lead ECG
- Vital signs (BP, HR)
- Laboratory safety assessments (hematology, chemistry, and urinalysis) (see Section 9.6.3.1)
- PSA
- Testosterone
    - Note for testosterone: In a subset of approximately 300 subjects, additional determination of total and free testosterone will be performed at screening and repeated every 6 months (Visit 3, Visit 5, etc.), and at the EOT Visit using a LC–MS/MS method for the analysis of total testosterone. The non–protein–bound (free) testosterone will be analyzed and calculated with the SHBG and albumin concentrations, both of which will also be determined
- A blood (plasma) sample for tumor–related biomarker analysis (genetic and non–genetic) unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities
- Whole blood draw sample for CTC analysis

- Optional collection of biopsy tissue taken at disease progression, if available, for tissue biomarker analyses unless precluded by local guidelines, e.g. IEC/IRB or regulatory authorities
- ECOG PS
- Date of first SSE (if applicable)
- Current medical condition, AEs, SAEs and concomitant treatments

Note: For all visits where questionnaires are administered, the questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

Active Follow–up Visits

After treatment discontinuation, subjects will begin the Active Follow–up period. Active Follow–up visits occur as standard of care clinic visits approximately every 12 weeks for up to 1 year to collect the following:

- Medical resource use
- Review handheld device or tablet and ensure subjects complete the following:
    - Symptom / QoL questionnaire NCCN–FACT–FPSI–17
    - Pain questionnaire – BPI–SF
    - Analgesic consumption log –eCRF (Physician to record whether or not the subject has initiated opioid therapy since last visit and to record analgesic pain meds consumed by the subject over last 24 hours). Should be collected on the same day as pain assessment questionnaires
    - To facilitate assessment of analgesic use, subjects should be requested to bring all pain medication consumed to each visit
- Record SSEs if applicable
- Subsequent antineoplastic treatments for prostate cancer which should be provided with start and stop dates and reason for treatment change (PSA progression, clinical progression, radiological progression, toxicity, other)
- Record survival status
- Study drug–related SAEs with concomitant medications received

Note: For all visits where questionnaires are administered, the questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

After approximately 1 year of Active Follow–up, subjects will be transitioned to Long–term (survival) Follow–up. The Active Follow–up period extends from the discontinuation of treatment period for up to 1 year or until the subject can no longer travel to the clinic, dies, is lost to follow–up, or withdraws IC and actively objects to collection of further data.

After primary analysis of the study, all subjects in the Active Follow-up will complete the study.

9.2.4 Long–term (survival) Follow–up period

After completing the Active Follow–up period, subjects will enter the Long–term Follow–up period. Subjects will be contacted approximately every 12 weeks by phone, and additional contacts may be required for overall (survival assessment). The following information will be collected:

- Record subsequent antineoplastic treatments for prostate cancer with start and stop dates and reason for treatment change (PSA progression, clinical progression, radiological progression, toxicity, other)
- Record survival status
- Study drug–related SAEs with concomitant medications received

As this information will be collected over the telephone from the subject, it is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the subject and document it in the eCRF.

After primary analysis of the study, all subjects in the Long-term Follow-up will complete the study.

9.2.5 Unscheduled visits

In the event that there are significant abnormal safety findings or suspected disease progression, control assessments may be performed at any time during the study treatment period according to the judgment of the Investigator. The following procedures (one or more) may be performed at the unscheduled visit, if indicated:

- Physical examination including weight
- 12–lead ECG
- Vital signs (BP, HR)
- Laboratory safety assessments (hematology, chemistry, urinalysis)
- Status of survival
- AEs, SAEs, current medical condition, concomitant treatments
- Chest, abdomen, and pelvic CT/MRI
- Bone scan

Other unscheduled procedures may be performed, as per Investigator's judgment.

The laboratory tests routinely obtained before each cycle of docetaxel must be reported in the unscheduled hematology and biochemistry eCRF.

For every formal analysis of OS, survival data will be collected through additional survival sweeps. All subjects considered alive at the database cut-off date and prior to any subsequent additional analysis will be contacted for survival status.

9.3 Population characteristics

9.3.1 Demographic

Demographic characteristics of date of birth (age), sex, and race/ethnicity should be entered in the eCRFs.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the ICF
- Considered relevant to the study

Detailed instructions on the differentiation between medical history and AEs can be found in Section 9.6.1.1.

History of prostate cancer will be collected separately from the general medical history. This includes, but is not limited to:

- Date of diagnosis
- Staging (performed at diagnosis)
- Prostate cancer history
- Disease status at study entry
- Prior diagnostic and therapeutic procedures
- Prior prostate cancer treatments (any therapy that is ongoing should be reported as concomitant medication)

9.3.3 Other baseline characteristics

Baseline characteristics relating to disease factors include:

- QoL assessment (NCCN–FACT FPSI–17)
- ECOG PS
- Cancer pain assessment

All medications and significant non–drug therapies ongoing during the screening period (28 days prior to randomization) must be entered in the eCRF, including:

- Medication trade name and dose
- Reason for medication
- Start date and end date, or if continuing at time of study entry

9.4 Efficacy

The primary efficacy variable is OS.

Survival status will be assessed from randomization until the end of the Long–term Follow-up period. Date of death and primary cause of death will be recorded.

For definition and analysis of primary variable, and for description of secondary and exploratory variables, please refer to Section 10.3.

9.5 Pharmacokinetics/pharmacodynamics

9.5.1 Drug measurements

The concentrations of diastereomers (*S,R*)-darolutamide (BAY 1896951) and (*S,S*)-darolutamide (BAY 1896952), metabolite keto-darolutamide (BAY 1896953) and docetaxel in plasma will be determined by a validated method, e.g. liquid chromatography–tandem mass spectrometry (LC–MS/MS). Darolutamide (BAY 1841788) concentration will be calculated as the sum of diastereomers (*S,R*)-darolutamide and (*S,S*)-darolutamide concentrations.

PK samples will be collected from all subjects to maintain blinding. However PK samples from the placebo arm will not be analyzed.

In the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, detailed mandatory blood sampling for PK analysis of darolutamide, (*S,S*)-darolutamide, (*S,R*)-darolutamide, keto-darolutamide, and docetaxel will be collected on the day of the first docetaxel administration which should be at least 14 days after randomization (i.e. start of study drug).

On this day blood samples will be collected at the following time points:

Pre–dose (prior to the administration of study drug and docetaxel), 20±10 minutes after start of docetaxel infusion, 1 hour (within 5 minutes before the end of infusion), 90 minutes, 2, 3, 4, 6, and 8 hours following the start of docetaxel infusion. For planned time points between 90 minutes and 8 hours, blood samples should be collected within ±15 minutes of the planned time.

Two additional samples will be taken at 2 subsequent docetaxel cycles (i.e. one sample per docetaxel cycle, at any time relative to study drug administration and after docetaxel administration on the same day), from docetaxel cycle 2 onwards. These samples will be used to provide information on variability at steady state for darolutamide and to explore any potential effect of darolutamide on the PK of docetaxel.

It is of importance that the actual date and time of blood sampling and study drug administration as well as docetaxel administration are documented in the eCRF because PK calculations will be based on the actual sampling times relative to dosing times.

In all other randomized subjects, sparse sampling for population PK will be collected to determine the exposure (i.e. area under the curve over the dosing interval at steady state) of darolutamide, the diastereomers (*S,S*)-darolutamide and (*S,R*)-darolutamide, the metabolite keto-darolutamide, and docetaxel and to quantify its variability in the target subject population.

Two samples will be taken on the day of first study drug intake (Visit 1 Day 1), at least 30 minutes after the first dose of study drug, approximately 1 hour apart to determine darolutamide absorption data.

Two additional samples will be taken at 2 docetaxel cycles (i.e. one sample per docetaxel cycle from the first cycle onwards, at any time relative to study drug administration and after docetaxel administration on the same day). These samples will be used to provide information on variability at steady state for darolutamide and to explore any potential effect of darolutamide on the PK of docetaxel. The first additional sample in this subset of subjects can be taken on the day of first docetaxel cycle, as long as the subject has already received at least one dose of study drug on the day before.

Drug intake and sampling times have to be accurately documented.

The instructions for sample collection, processing, storage and shipment will be detailed in a separate document (e.g., sample handling sheet or lab manual).

9.5.2 Pharmacokinetic evaluation

Non–compartment approach PK analysis

In the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel:

Pharmacokinetic parameters will be calculated using a non–compartment approach according to the current Bayer guidelines, using Win–Nonlin software. Details of the used version will be given in the clinical study report.

Based on the plasma concentration–time data, the following PK parameters are planned to be estimated for darolutamide, (*S,S*)-darolutamide, (*S,R*)-darolutamide, keto-darolutamide, and docetaxel.

Main parameter:

Darolutamide, (*S,S*)-darolutamide, (*S,R*)-darolutamide, keto-darolutamide:

AUC(0–12) [1)]

1) : Using the predose plasma sample also as 12 hour sample

Docetaxel**:**

AUC(0–t_{last})

Additional parameters:

Darolutamide, (*S*,*S*)-darolutamide, (*S,R*)-darolutamide, keto-darolutamide:

AUC(0–8), AUC(0–t_{last}), C_{max}, t_{max}, t_{last}

Docetaxel**:**

C_{max}, t_{max}, t_{last}

To ensure the blinding of the PK–evaluator during preliminary PK evaluation for DMC review, concentration data with masked subject IDs will be provided by Bioanalytics. The evaluation results will then be transferred to an unblinded statistician at the DMC.

Population PK evaluation

In all other randomized subjects:

Individual concentration–time data of darolutamide, (*S*,*S*)-darolutamide, (*S,R*)-darolutamide, and keto-darolutamide will be provided in a clinical study report appendix. The concentration data from this study, which might be augmented with PK data from other studies, will be analyzed to evaluate the variability of the PK of darolutamide, of the respective diastereomers (*S*,*S*)-darolutamide and (*S,R*)-darolutamide, and of the metabolite keto-darolutamide in this phase III population. The possible effect of relevant covariates on the PK of these compounds might also be evaluated. In addition, exploratory exposure–response analyses of efficacy, PD or safety parameters, e.g. OS, PSA response rate, etc., are planned. In addition, the docetaxel exposure in the two treatment groups will be compared. A population PK approach will be applied for these evaluations, which will be described in detail in a separate Modeling & Simulation (M&S) Plan and the results will be reported separately in the M&S Report.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a subject or clinical investigation subject after providing written IC for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG results.

- Conditions that started before signing of IC and for which no symptoms or treatment are present until signing of IC will be recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of IC and for which symptoms or treatment are present after signing of IC, at unchanged intensity, will be recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of the ICF including those recorded as medical history will be documented as AEs. This includes intercurrent illnesses.

Definition of a serious adverse event

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria:

a. Results in death

b. Is life threatening

The term 'life threatening' in the definition refers to an event during which the subject was at risk of death at the time of the event. It does not refer to an event that, hypothetically, might have caused death if it were more severe.

c. Requires in–subject hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre–planned
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (e.g. social hospitalization for purposes of respite care)

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE, dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability/incapacity

Disability means a substantial disruption of a person's ability to conduct normal life functions.

e. Is a congenital anomaly/birth defect

f. Is another medically important serious event as judged by the Investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the Investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The severity (or intensity) of AEs should be documented using NCI–CTCAE v 4.03. If no exact matching code is available in NCI–CTCAE v 4.03, the following guide should be used:

- CTC 1 = Mild AE: Transient in nature and generally not interfering with normal activities
- CTC 2 = Moderate AE: Sufficiently discomforting to interfere with normal activities
- CTC 3 = Severe AE: Prevents normal activities
- CTC 4 = Life threatening (subject was at risk of death at the time of the event)
- CTC 5 = Results in death (fatal)

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF. The causal relationship should be assessed to darolutamide/placebo as well as the background docetaxel treatment independently.

The assessment is based on the question whether there was a “reasonable causal relationship” to darolutamide/placebo or docetaxel in question.

Possible answers are “yes” or “no.”

An assessment of “no” should include either:

1. The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)

   or

2. A lack of plausibility (e.g. the subject is struck by an automobile without evidence that darolutamide/placebo or docetaxel caused disorientation that may have led to the event, or cancer develops a few days after the first administration of a darolutamide/placebo or docetaxel.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of darolutamide/placebo or docetaxel.

Important factors to be considered in assessing the relationship of the AE to darolutamide/placebo or docetaxel include:

- The temporal sequence relating the event to drug administration. The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (dechallenge) and recurrence on drug re–introduction (rechallenge). The subject's response after dechallenge or the subject's response after rechallenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of these may be suspected as a cause for the event in question.
- Known response pattern for this class of drug: Clinical/preclinical.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study treatment: The PK properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's PD should be considered.
- The assessment is not possible.

Causal relationship to protocol–required procedure(s)]

The assessment of a possible causal relationship between the AE and protocol–required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol–required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below:

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

9.6.1.2.5 Other specific treatment(s) of adverse events

- None

- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented using the following categories:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

All AEs occurring from the time the subject has signed the ICF until 30 (+7) days after the last dose of study drug must be entered in the subject's eCRF. All treatment–emergent AEs must be followed until resolution or stabilization, wherever feasible.

The type of information that should be assessed and recorded by the Investigator for each AE is listed in Section 9.6.1.2.

Disease progression per se should not be regarded as an AE. Instead, the associated signs and symptoms should be recorded as AEs.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all SAEs, the Sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study drug.

A laboratory test abnormality that is considered to have a clinically relevant effect on the subject (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Investigator) should be reported as an AE.

Documentation of an AE must be supported by an entry in the subject's medical file.

Each event should be described in detail, along with start and stop dates, severity, relationship to investigational product, action taken, and outcome.

9.6.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the Sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the Investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the Investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 9.6.1.1 must immediately (within 24 hours of the Investigator's awareness) be reported to the recipient detailed in the Investigator's file. An SAE form must also be completed within 24 hours of the Investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Serious AEs that occur 30 (+7) days after the last dose of study drug during Active Follow–up or Long–term Follow–up should be reported on the SAE form, if the Investigator feels that there is a reasonable possibility for the event to have been caused by the study subject's participation in the study. In such cases, the SAEs will be processed by the Sponsor according to all applicable regulations.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (e.g. hospitalization), the associated signs and symptoms may be reported as an SAE, but the underlying cause (that is, "recurrent disease" or "metastatic disease") should not be reported as an SAE. In this case, recurrent or metastatic disease should be mentioned on the SAE form as an "alternative explanation."

An isolated laboratory abnormality that is assigned a severity rating of Grade 4, as defined in NCI–CTCAE v 4.03, is not reportable as an SAE unless the Investigator assesses that the event meets standard International Conference on Harmonization criteria for an SAE. Similarly, a baseline laboratory abnormality that is part of the disease profile should not be reported as an SAE when assigned a severity rating of Grade 4, as defined in NCI–CTCAE v 4.03, specifically when this abnormality is allowed (or not excluded) by the protocol inclusion/exclusion criteria (see Sections 6.1 and 6.2). If an Investigator is in doubt about the applicable reporting obligations, he/she should consult with the study monitor for the Sponsor. The NCI–CTCAE version 4.03 Grade 4 laboratory abnormalities will be documented and will be reviewed on a regular basis.

Notification of the IECs / IRBs

Notification of the IECs/IRBs about all relevant events (e.g. SAEs or SUSARs) will be performed by the Sponsor/delegate and/or by the Investigator according to all applicable regulations.

Notification of the authorities

The Sponsor will expedite all suspected unexpected SAEs and SUSARs as well as other safety issues requiring expedited reporting to the relevant authorities within applicable timelines.

Sponsor's notification of the investigational site

The Sponsor/delegate will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the Sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Adverse events of special safety interest

None.

9.6.2 Pregnancies

Sexually active male subjects 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 3 months after the end of the treatment with darolutamide, and 6 months after treatment with docetaxel (inclusion criterion).

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

For a pregnancy in the partner of a male study subject, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

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.

9.6.3 Further safety

9.6.3.1 Laboratory safety assessments

The PSA and testosterone values are to be assessed by a central laboratory during the study period. Blood samples to test alkaline phosphatase for stratification purpose will be analyzed in central laboratory and thereafter by local laboratory. Other laboratory assessments are to be performed by local laboratories.

Instruction on sample collection, handling, labeling, storage, and shipment will be provided in the laboratory manual.

The following laboratory safety assessments will be performed during the screening period, study treatment period and at the end–of–study treatment visit.

At screening, all the following assessments are to be taken within 7 days prior to randomization, but PSA.

Hematology:

- Hemoglobin
- Hematocrit
- Erythrocyte count
- Leukocyte count
- Differential count (lymphocytes, monocytes, eosinophils, neutrophils, basophils)
- Mean corpuscular hemoglobin
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration
- Thrombocytes

Chemistry:

- Albumin
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
    - Note: Blood samples to test alkaline phosphatase for stratification purpose will be analyzed in central laboratory and thereafter by local laboratory
- Bilirubin total (+ direct and indirect bilirubin if total bilirubin is >1.0 x ULN)
- Calcium
- Blood urea nitrogen
- Creatinine
- Serum glucose
- Total protein
- Lactate dehydrogenase
- Potassium
- Sodium
- Testosterone
    - Note for testosterone: In a subset of approximately 300 subjects, additional determination of total and free testosterone will be performed at Screening and repeated every 6 months (Visit 3, Visit 5, etc.), and at the EOT Visit using a LC–MS/MS method for the analysis of total testosterone. This method allows precise quantification of low testosterone levels in subjects during ADT

treatment. The non–protein–bound (free) testosterone will be analyzed and calculated with the sex hormone–binding globulin (SHBG) and albumin concentrations, both of which will also be determined

- PSA (total) (at screening, blood sample for PSA is to be taken within 28 days prior to randomization)
- Chromogranin A (only at Screening)
- Prothrombin time, expressed as international normalized ratio, in subjects under vitamin K antagonist therapy (local assessment)

Urinalysis:

- Glucose
- Protein
- Erythrocytes
- Leukocytes

Safety assessments for docetaxel: Hematology (for ANC check), ALT, AST, bilirubin total (+ direct and indirect bilirubin if total bilirubin is >1.0 x ULN) are mandatory safety assessments to be checked before each cycle of docetaxel. Further laboratory safety assessments may also be checked according to Investigator's judgment.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the Investigator will be informed to determine follow–up activities outside of this protocol.

9.6.3.2 Physical examination

Physical examination will be performed and weight will be measured at all visits (except at Day 1 Visit if already performed at Screening). Height will be recorded at Screening only.

Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.6.1.1).

9.6.3.3 12–lead ECGs

All 12–lead ECGs will be recorded in a supine position after at least 10 minutes rest.

9.6.3.4 Vital signs

All vital sign assessments will be recorded in a supine position after at least 10 minutes rest.

9.7 Other procedures and variables

Other exploratory variables in this study are pain intensity and pain interference scores from the BPI–SF, medical resource use, and assessment of biomarkers.

In addition to calculating a pain score based on the worst pain question (i.e., worst pain subscale [WPS] score) on the BPI–SF (Appendix 16.4), the subject's responses on the BPI-SF can be used to calculate a pain score intensity and a pain interference score (29).

9.7.1 Biomarker investigations

Biomarker status will be correlated with clinical outcome to explore whether any biological targets appear to define subject populations that are particularly sensitive or resistant to darolutamide. Details of the biomarker analyses may be described in a separate statistical analysis plan (SAP) and the results of these analyses may be provided as a separate biomarker report.

Tumor biomarker studies will be performed to investigate the mechanisms by which darolutamide may work in subjects with mHSPC and will use tumor biomarkers circulating in plasma or, if available, biopsies either collected prior to study entry or at disease progression.

Tumor biomarkers may be categorized as "non–genetic" (involving protein) or "genetic" (involving ribonucleic acid [RNA] or deoxyribonucleic acid [DNA]). In the current study, analyses of both non–genetic and genetic biomarkers are planned. The analysis of tumor genetic markers by tumor DNA sequencing and/or gene expression studies with tissue samples taken from the primary tumor and metastases will support identification of biomarkers contributing to clinical benefit to therapy. Utmost care will be taken to protect subject identity during biomarker analyses.

Biomarkers related to drug safety, efficacy, or mechanism of action will be analyzed from whole blood and involve targeted genetic testing. Targeted genetic testing will focus on single gene polymorphisms of genes involving, but not limited to, hepatotoxicity, metabolism, or targets involved in drug activity. Identified gene variants aim to predict the best individuals to treat, either selecting for toxicity avoidance or for positive benefit.

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and / or literature data.

Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual).

9.7.1.1 Plasma–based biomarker analysis

Subjects will be asked to provide blood samples for biomarker analyses, which will be obtained during regular study visits in which blood will be drawn for other scheduled but unrelated laboratory tests.

Genetic biomarkers from plasma:
These samples are intended to isolate plasma to study tumor markers circulating in blood such as circulating tumor DNA (ctDNA) or circulating tumor RNA. Candidates of genes for the evaluation from ctDNA are AR, PIK3CA, and phosphatase and tensin homolog (PTEN). The types of analyses may comprise the identification of mutations or splice variants.

Furthermore, these plasma samples will serve as source for non–coding microRNA, as possible markers describing treatment response.

Non–genetic biomarkers from plasma:
Plasma samples will also be used to quantify the circulating levels of various proteins of interest, to attempt to identify a protein signature that correlates with drug response.

Plasma samples for the analyses of tumor biomarkers (genetic and non–genetic biomarkers) will be prepared from blood samples obtained at the following time points:

- Screening visit and on Day 1, Visit 1 (pre–dose) once eligibility criteria have been confirmed
- Visit 2 and subsequent Visits
- End of Treatment Visit

On treatment days, blood will be drawn for preparation of plasma samples prior to drug administration, if possible.

In addition to the proteins and genes listed above, other biomarkers deemed relevant to this study will be measured.

Data from the biomarker analyses may be correlated with measures of clinical efficacy or toxicity obtained in this study.

9.7.1.2 Circulating tumor cells

CTCs may serve as source of tumor metastases circulating in blood and may reflect the tumor phenotype or genotype. Enumeration of CTCs may serve as description of tumor burden.

Circulating tumor cells will be analyzed in detail from whole blood samples collected at various time points to assess the effect of darolutamide in decreasing numbers of CTCs as well as to characterize the phenotype and genotype of CTCs such as presence of AR mutations, AR splice variants, and other genomic markers.

A whole blood sample for CTC analysis will be obtained at Visit 1 (once eligibility criteria have been confirmed), Visit 2 and EOT.

9.7.1.3 Tumor–based biomarker analysis

From subjects for which tumor tissue specimens (e.g. from biopsy) are available, tumor specific biomarker analyses are intended to be used for the following purposes: (1) to evaluate mutations, copy numbers or gene rearrangements in known oncogenes such as AR, TMPRSS, cMYC, PI3K, and CYP17 extracted from tumor tissue specimens; (2) to analyze the gene expression of genes of interest such as AR, cMYC, PTEN, PI3K, and AR–regulated genes in RNA extracted from tumor tissue specimens; (3) to evaluate expression of non–coding tumor relevant RNAs such as microRNAs.

Provided sufficient tissue quality and quantity, tumor tissue specimens are also intended to be used to quantify the expression of proteins of interest, to attempt to identify a protein signature that correlates with drug response.

As per Investigator's discretion, and if technically feasible, biopsy at the time of disease recurrence is highly encouraged to be taken. This sample would allow generation of information about the identification of tumor biomarkers playing a role in therapy resistance for which the subject may benefit for further guidance. Note, however, that this is not considered to be mandatory by this study protocol.

9.7.1.4 Genetic biomarker analysis from whole blood

Biomarkers related to drug safety, efficacy, or mechanism of action may be analyzed from whole blood and involve targeted pharmacogenetic testing. These studies will conducted aiming to find gene variants associated with responses to darolutamide treatment and to predict the best individuals to treat, either selecting for toxicity avoidance or for positive benefit.

Targeted pharmacogenetic testing will focus on single gene polymorphisms (SNPs) on genes involved but not limited to hepatotoxicity, metabolism, or targets involved in drug activity.

Unless precluded by local guidelines, subjects will be asked to sign a separate pharmacogenetic ICF. A whole blood sample for pharmacogenetic testing will be obtained preferably at Visit 1 (once eligibility criteria have been confirmed) or alternatively at any other visit during the treatment period, regardless of the time of study drug intake. Samples can only be collected from subjects who have signed a separate pharmacogenetic ICF. From these blood samples, DNA will be isolated which will be used for the analysis SNP candidates such as CYP17.

9.7.2 Medical resource use

Information on medical resource use (e.g. hospitalization visits, physician visits etc.) that is associated with the management of AEs as well as non–protocol–driven subject monitoring will be collected by e–CRF that is completed by the physician at each visit.

9.7.3 Subject–reported outcomes

For this study, health–related QoL will be measured using the NCCN–FACT FPSI–17 questionnaire.

The NCCN–FACT FPSI–17 is a validated instrument that was developed to assess symptoms of prostate cancer, symptoms of treatment of prostate cancer, and health related QoL of prostate cancer subjects. The instrument was developed in accordance with recent Food and Drug Administration guidance for development of instruments for ePRO. The instrument contains 17 items, each of which utilizes a Likert scale with 5 possible responses (30). The 10 items reflect disease–related physical symptoms of disease and the responses on the items are to be summed to calculate a disease–related physical symptom subscale score. One item represents emotional symptoms of disease and the response to that item is used to calculate a disease–related emotional symptom subscale score. Four items represent treatment–related symptoms and the responses to these items are summed to calculate a treatment side effect subscale score. Finally, 2 items represent functional well–being and responses to those items are summed to calculate a functions / well–being subscale score. The NCCN–FACT FPSI–17 will be self–administered by the subject via ePRO device. Some subjects may skip an item

altogether if they feel that it is not applicable to them. The questionnaire is to be completed at baseline either within 7 days before randomization or at Visit 1 (Day 1), at all treatment visits (at Visit 2 and subsequent visits), at the End of Treatment (EOT), and approximately every 12 weeks during Active Follow–up.

Brief Pain Inventory – Short form is a validated instrument totaling 15 items to assess subject–reported levels of pain that has a precedent of being used in clinical trials with the goal of obtaining label claims based on the results captured with this instrument. A reduced set of 11 items is used in this trial. This reduced questionnaire is self–administered and designed to evaluate the intensity of, and the impairment caused by, pain. All BPI–SF items are scored using rating scales. Four items measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 (“no pain”) to 10 (“pain as bad as you can imagine”) numeric rating scales, and 7 items measure the level of interference with function caused by pain (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales.

The items are aggregated into 2 dimensions: (1) Pain severity index, using the mean of the 4 items on the pain intensity, and (2) Function interference index, using the mean of the 7 pain interference items. All 4 severity items must be completed for aggregating the pain severity index. The function interference index is scored as the mean of the item scores multiplied by 7, given that more than 50% or 4 of 7, of the items have been completed.

The questionnaire is to be completed via ePRO at Baseline (Screening or Visit 1), at treatment visits (at Visit 2 and subsequent visits), at EOT, and approximately every 12 weeks during Active Follow–up.

For each questionnaire, a subject–reported outcome (PRO) information sheet must be completed by the study nurse/Investigator at each visit at which the questionnaires are scheduled to be administered regardless of whether or not the questionnaires were completed, in order to document information on questionnaire assessment such as completion status, date of administration, and reasons for non–completed questionnaires, missing assessments, etc.

9.8 Appropriateness of procedures / measurements

All efficacy and safety parameters, as well as the methods to measure them, are standard variables /methods in clinical studies and/or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant.

The NCCN–FACT FPSI–17 is a validated instrument that was developed to assess symptoms of prostate cancer, symptoms of treatment of prostate cancer, and health related QoL of prostate cancer subjects (28).

Brief Pain Inventory – Short form is validated to assess subject–reported levels of pain that has a precedent of being used in clinical trials with the goal of obtaining label claims based on the results captured with this instrument.

The NCI–CTCAE v 4.03 is a list of AE terms harmonized with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology at the AE term level and associated with a severity grading scale that is widely used within the oncology research community as the

standard for documentation and analysis of AEs occurring in cancer research. This tool is useful in defining the maximum tolerated dose of study drugs, in making recommendations concerning modification of dose and dose schedule of study drugs, and in comparing safety profiles of therapeutic interventions.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using SAS; the version used will be specified in the SAP.

10.2 Analysis sets

Full analysis set (FAS): All randomized subjects. The FAS will be used in the analysis of all efficacy endpoints. Subjects will be included in FAS according to the treatment to which they are randomized.

Safety analysis set (SAF): All randomized subjects who have received at least 1 dose of study drug. This safety population will be used in the analyses of all safety endpoints. Subjects will be included in the analyses according to the treatment they actually received.

Pharmacokinetic Analysis Set (PKS): The first 20 subjects who were randomized and have received at least 1 cycle of docetaxel, and for whom mandatory dense PK sampling will be done, will be included in the Pharmacokinetic Analysis Set, as long as they have received at least 3 days of uninterrupted study drug treatment as well as one cycle of docetaxel and have at least one post dose PK measurement.

10.3 Variables and planned statistical analyses

The complete list of variables to be analyzed for this study will be provided in the SAP.

10.3.1 Primary efficacy variable

The primary efficacy variable is OS, defined as the time (in days) from date of randomization until death from any cause.

Analysis of OS

All randomized subjects (FAS) will be included in the primary analysis of OS, the primary efficacy endpoint. The analysis will be performed when approximately 509 deaths are observed. The primary analysis of OS will be a stratified log–rank test with the same stratification factors as used for randomization.

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

The HR (darolutamide group/placebo) for OS and its 95% confidence interval will be calculated using the Cox model, stratified by the same factors as stated above. Kaplan–Meier

(KM) estimates for OS will be presented for each treatment group. The KM estimates at time points such as 3 months, 6 months, etc., together with corresponding 95% confidence intervals (CIs) and the differences of these estimates between the darolutamide group and the placebo group will be presented.

The overall one–sided type I error rate for the analysis of OS is 0.025. One formal interim analysis of OS for futility was planned. A DMC was overseeing the interim analysis. For further details on the interim analysis, see Section 10.5.

10.3.2 Secondary efficacy variables

The secondary efficacy variables include:

- **Time to castration–resistant prostate cancer**, defined as the time to PSA progression (Section 10.3.4) with serum testosterone being at castrate level <0.50 ng/mL, or the time to progression by soft tissue/visceral lesions (as described in Section 9.2.2.3) or time to progression by bone lesions (as described in Section 9.2.2.3), whatever comes first.
- **Time to initiation of subsequent antineoplastic therapy**, defined as the time from randomization to initiation of first subsequent antineoplastic therapy for prostate cancer.
- **Symptomatic skeletal event free survival**, defined as the time from randomization to the first occurrence of SSE or death from any cause, whichever comes first. An SSE is defined as EBRT to relieve skeletal symptoms, or new symptomatic pathologic bone fracture, or occurrence of spinal cord compression or tumor–related orthopedic surgical intervention, whichever comes first.
- **Time to first SSE**, defined as the time from randomization to the first occurrence of SSE. An SSE is defined as EBRT to relieve skeletal symptoms, or new symptomatic pathologic bone fracture, or occurrence of spinal cord compression or tumor–related orthopedic surgical intervention, whichever comes first.
- **Time to initiation of opioid use for ≥7 consecutive days**, defined as the time from date of randomization to the date of first opiate use for ≥7 consecutive days. Time to opiate use will be determined by opioid use captured via eCRF (recorded opioid, see schedule of assessments).
- **Time to pain progression is defined as** the interval from randomization to the first date a subject experiences a pain progression. Pain will be assessed with the BPI–SF questionnaire (Appendix 16.4) during the visit, prior to any procedures or examination by physician. Subjects who have not experienced pain progression at the time of analysis will be censored on the last date the subject was known to have not progressed. Subjects with no on study assessment or no baseline assessment will be censored at the date of randomization.

For **asymptomatic subjects** (WPS 0 at baseline), pain progression is defined as an increase of 2 or more points in the "worst pain in 24 hours" (i.e. 2 or more point increase in WPS score) score from baseline observed at 2 consecutive evaluations ≥4 weeks apart

OR

initiation of short– or long–acting opioid use for pain.

For **symptomatic subjects** (WPS >0 at baseline), pain progression is defined as an increase of 2 or more points in the "worst pain in 24 hours" (i.e. 2 or more point increase in WPS score) score from baseline observed at 2 consecutive evaluations ≥4 weeks apart and a WPS of ≥4

OR

initiation of short– or long–acting opioid use for pain.

- **Time to worsening of physical symptoms of disease** is defined as the interval from randomization to the first date a subject experiences an increase in physical symptoms based on the NCCN–FACT–FPSI–17 questionnaire. Symptoms and QoL will be assessed with the NCCN–FACT–FPSI–17 questionnaire (Appendix 16.3) during the visit, prior to any procedures or examination by physician. An increase in physical symptoms of disease is defined as 3–point decrease (a lower score = higher symptom burden) from baseline in the physical symptoms of disease subscale (FPSI–DRS–P subscale of the NCCN–FACT–FPSI–17 questionnaire) observed at 2 consecutive evaluations ≥4 weeks apart.

Secondary efficacy variables analysis

The secondary efficacy variables will be analyzed for the FAS population unless otherwise specified in the SAP. Time–to–event endpoints will be analyzed using stratified log–rank test with randomization stratification factors. Hazard ratio and 95% CI will be provided using the Cox model stratified by the same factors as stated above. Detailed analysis methods and the plan for type 1 error control for secondary endpoints, including ranking of secondary endpoints, will be specified in the SAP.

10.3.3 Safety variables

The safety variables include:

- AEs until the end–of–study treatment visit
- SAEs until the end–of–study treatment visit
- Study drug–related SAEs until the end of Long–term Follow–up
- Vital signs: BP and heart rate (HR)
- 12–lead electrocardiogram (ECG)
- Physical examination
- Laboratory safety assessments (hematology, clinical chemistry, urinalysis)

Safety analysis

AEs will be coded using MedDRA. Descriptive summary tables will be presented on all safety parameters by treatment group. The safety assessment period is from the first dose of study drug until 30 days (+7 days) after the last treatment with darolutamide/placebo. Subjects will be monitored for AEs using the NCI–CTCAE v 4.03.

The AEs and safety laboratory parameters will be presented with their worst NCI–CTCAE v 4.03 grade (Section 16.2).

10.3.4 Other exploratory variables

- **Rate of absolute PSA response at 6 and 12 months**

  Absolute PSA response is defined as blood PSA level <0.2 ng/mL, confirmed by a second subsequent PSA value <0.2 ng/mL 3 or more weeks later. Rate of absolute PSA response is defined as the number of subjects with absolute PSA response, divided by the total number of subjects evaluable for absolute PSA response. Rate of absolute PSA response will be evaluated on subject data up to 6 months and 12 months after randomization.

- **Rate of relative PSA response at 3, 6 and 12 months**

  Relative PSA response is defined as a ≥30% reduction of the blood PSA level compared to the screening value, confirmed by a second subsequent PSA value with a ≥30% reduction from Screening 3 or more weeks later. Rate of relative PSA response is defined as the number of subjects with relative PSA response, divided by the total number of subjects evaluable for relative PSA response. Rate of relative PSA response will be evaluated on subject data up to 3 months, 6 months, and 12 months after randomization.

- **Time to PSA progression**

  Prostate–specific antigen progression is defined as a ≥25% increase above the nadir (lowest Screening or baseline) value, which is confirmed by a second value 3 or more weeks later, and an increase in absolute value of ≥2 ng/mL above nadir, at least 12 weeks from baseline.

  The time to PSA progression is defined as the time (in days) from the date of randomization to the date of first PSA progression. Subjects without PSA progression as of database cut–off, whether or not surviving, will be censored at the last total PSA lab assessment date.

- **Changes in symptom burden and QoL based on the NCCN–FACT FPSI–17 questionnaire** (see Section 10.3.8)
- **Medical resource use** (see Section 9.7.2)
- **Pharmacokinetics** (see Section 9.5.2)
- **Biomarker evaluations** (see Section 9.7.1)

The details of the analysis for the exploratory variables to be analyzed for this study will be provided in the SAP.

Missing data / drop outs

Every effort should be made to retain subjects who discontinue the treatment period for any reason. These subjects are to be encouraged to remain on the study for follow–up of primary, secondary, and exploratory endpoints.

The method used for imputation of missing data will be described in the SAP (see Section 11.4).

10.3.5 Pharmacokinetics

Pharmacokinetics in the first 20 subjects who were randomized and have received at least 1 cycle of docetaxel

The concentration–time courses of all substances will be tabulated separated by treatment. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation (SD), and coefficient of variation (CV); geometric mean, geometric SD (re–transformed SD of the logarithms), and CV; minimum, median, maximum value, and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one–half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration versus time curves of all substances (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted by treatment using both a linear and semilogarithmic scale.

Pharmacokinetic characteristics (t_{max}, t_{last} excluded) will be summarized by the statistics mentioned above. The t_{max}, t_{last} will be described utilizing minimum, maximum, and median as well as frequency counts.

Pharmacokinetics in all subjects

Individual concentration–time data of darolutamide, (*S,S*)-darolutamide, (*S,R*)-darolutamide, and keto-darolutamide will be provided in a clinical study report appendix. All other parameters will be described in detail in a separate M&S report.

10.3.6 Biomarker analyses

Results from exploratory biomarker studies will be reported in a separate biomarker report.

10.3.7 Medical Resource use

Medical resource use is described in Section 9.7.2.

10.3.8 Subject–reported outcomes

Subject–reported outcome procedures are described in Section 9.7.3.

10.3.9 Baseline and demographic characteristics

Baseline and demographic characteristics will be summarized by descriptive statistics by treatment group darolutamide for the FAS population.

In addition, exploratory exposure–response analyses of efficacy, PD, or safety parameters, e.g. OS, PSA response rate, etc., are planned.

10.4 Determination of sample size

The sample size of the study is based on the primary endpoint of OS. The study is designed to have 90% power to detect a 33% increase in median time of OS with darolutamide compared to placebo (from 60 to 80 months, corresponding to a HR of 0.75) with a 1–sided alpha of 0.025. The OS data will be considered as mature when approximately 509 deaths are observed.

With the additional assumptions that subjects will enroll at a rate of 50 subjects per month, exponential distributions of the OS event times, median time of OS in the control group of 60 months, 5% dropout rate of subjects, and a 6–months enrollment ramp–up period, it follows that approximately 1,300 subjects must be enrolled to observe 509 deaths after approximately 70 months.

10.5 Planned interim analyses

One formal interim analysis of OS was planned. This interim analysis for futility was to be performed after approximately 153 deaths were observed. The DMC (see Section 13.1.1) was overseeing the interim analysis. Detailed analysis methods and stopping rules will be specified in the SAP and the DMC charter.

For the futility interim and final analyses together, a one–sided overall beta of 0.1 will be used. Stopping boundaries will be calculated with an O'Brien–Fleming beta–spending function based on the actual number of events observed up to the cut–off date. The interim futility analysis was planned to be performed when approximately 153 deaths were observed (information fraction=0.3).

A DMC (see Section 13.1.1) will be instituted for independent review of ongoing data from this study in accordance with a separate DMC charter. The DMC will operate independently of the Sponsor and Investigators.

The DMC will review safety data as per a separate DMC charter.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be an eCRF; a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (CIE/TOSCA; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based electronic data capture (EDC) software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password–protected security system that is part of the RAVE software. All internal Bayer and external Investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE system contains a system–generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the Investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

It is the expectation of the Sponsor that key data entered into the CRF has source documentation available at the site. Study–specific data not needed for the subject’s routine medical care (QoL–related data: NCCN–FACT FPSI–17 and BPI–SF questionnaires) may be entered directly into the validated database or data system, without availability of corresponding source documentation.

The site must implement processes to ensure availability of all required source documentation. A source document checklist will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

Data recorded from screening failures

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At a minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth / age; sex; if applicable, race/ethnicity)
- Relevant Inclusion and/or Exclusion criteria
- Date of IC
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
    - Concomitant medication
    - Medical history
    - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and Sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The Sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate, and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol).
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable Sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IXRS, laboratory, ECG, ePRO, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, the clinical database is planned to be re–opened for the inclusion of the following additional data: PK data, antibody data.

11.4 Missing data

The analysis of the primary endpoint is based on the intent to treat population. Subjects who discontinue the treatment prematurely or leave the study prematurely will not be replaced.

Handling of missing data, which in this context are events not observed for the time–to–event endpoints (primary variable and secondary variables), is implicitly handled in the statistical methods applied (log–rank test, Cox model) by censoring these subjects. Further aspects of handling of missing data will be discussed in the SAP.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The Investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The Investigator should notify the Sponsor immediately of any such inspection.

The Investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Subject (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. Where the archiving procedures do not meet the minimum timelines required by the Sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The Investigator/institution notifies the Sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The Investigator site file is not to be destroyed without the Sponsor's approval.

The contract with the Investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The Sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due, but not limited to, the following reasons:

- If risk–benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (e.g. toxicity, teratogenicity, carcinogenicity, or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Investigator has the right to close his/her center at any time.

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 partial study closure, ongoing subjects, including those in post–study follow–up, must be taken care of in an ethical manner.

Details for an individual subject's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Sponsor's medical expert

Name: PPD
Address: Muellerstrasse 178
13353 Berlin, Germany
Telephone no.: PPD

Co–ordinating investigators

Name: PPD
Address: PPD
United States

Name: PPD
Address: PPD
Belgium

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's Investigator site file.

Whenever the term 'Investigator' is noted in the protocol text, it may refer to either the PI at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The PI of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, Sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the PI and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the Sponsor's study file.

The global Sponsor of this study is identified on the title page of this protocol. If required by local law, local co–sponsors will be nominated; they will be identified on the respective country–specific signature pages.

13.1.1 Independent data monitoring committee

A DMC will be instituted to ensure ongoing safety of study subjects with respect to a risk/benefit assessment during periodic data review meetings, review results from the planned interim analysis and provide a formal recommendation for continuation/termination of the study and monitor study conduct to ensure the overall integrity of trial is maintained. Recommendation for trial continuation will be guided by safety evaluations at all safety data reviews. The committee will include at least 3 independent oncologists and one independent statistician. Data review meetings will be held periodically as per separate DMC charter. Enrollment in the study will continue throughout the scheduled meetings of the DMC. Decisions on trial termination, protocol amendment, on hold of subject recruitment, or cessation of subject recruitment based on risk/benefit assessments will be made after recommendations from the DMC have been assessed by the Sponsor. Safety review meetings will be held in accordance with the DMC charter. Decisions on study termination or cessation of subject recruitment based on safety or OS outcomes will be made after recommendations from the DMC have been assessed by Bayer AG.

The DMC will also review the safety assessment, including PK, which will be performed after the first 20 subjects were randomized and have received at least 1 cycle of docetaxel. Blinding of Investigators, subjects and the Sponsor will be maintained during this assessment based on the preclinical mechanisms and known safety profiles for the darolutamide and docetaxel (see Section 3.3), the toxicities from the combination are expected to be manageable. Therefore, enrollment will continue during this 20–subject safety review unless unexpected or excessive toxicities related to darolutamide in addition to docetaxel plus ADT compared to the treatment of docetaxel plus ADT alone are reported, in which case subject enrollment will be placed on hold until completion of the DMC safety review. Further safety reviews to ensure subjects' safety may be implemented for different subject populations following the first 20 subjects who were randomized and have received at least one cycle of docetaxel, due to lack of experience in treatment of darolutamide in addition to docetaxel plus ADT. The details of the evaluations will be described in the DMC charter.

13.2 Funding and financial disclosure

Funding

This study will be funded by its Sponsor.

Financial disclosure

Each Investigator (including principal and/or any sub–investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the Sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the Sponsor or the Investigator without agreement by both parties. However, the Investigator or the Sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/Sponsor. Any deviations from the protocol must be explained and documented by the Investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and ICF provided by the Sponsor or the study center. A sample subject information and ICF is provided as a document separate to this protocol.

Based on this subject information sheet, the Investigator or designee will explain all relevant aspects of the study to each subject/legal representative or proxy consenter (if the subject is under legal protection) prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study–specific data is recorded on study–specific forms).

The Investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject/legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

- The subject's consent covers end–of–study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- Subject–specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The subject has the right to object to the generation and processing of this post–withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.

If at any time during the study the subject would like to withdraw consent, the Investigator must discuss with the subject the active and Long–term Follow–up period parts of the study. Withdrawal of consent should be documented in the subject's medical file.

Each subject/legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the Investigator will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed IC statement is to remain in the Investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that IC is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that IC was obtained prior to these procedures.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the Sponsor and the Investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The ICF and any other written information provided to subjects/legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written ICF. The Investigator will inform the subject/legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

13.5 Publication policy and use of data

The Sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the Sponsor will fulfill its obligations according to all applicable laws and regulations. The Sponsor is interested in the publication of the results of every study it performs.

The Sponsor recognizes the right of the Investigator to publish the results upon completion of the study. However, the Investigator, while free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the Sponsor on the intended publication manuscript before its submission. To this end, the Investigator must send a draft of the publication manuscript to the Sponsor within a time period specified in the contract. The Sponsor will review the manuscript promptly and will discuss its content with the Investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects / insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the IC process, the subjects will be informed in writing that representatives of the Sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject’s identity will remain confidential.

The Investigator will maintain a list to enable subjects to be identified.

14. Reference list

1. Ferlay J, Steliarova–Foucher E, Lortet–Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403.
2. Ferlay J, Parkin DM, Steliarova–Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010;46(4):765–81.
3. Jemal A, Thun MJ, Ries LA, Howe HL, Weir HK, Center MM, et al. Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst. 2008;100(23):1672–94.
4. National Cancer Institute. SEER Stat Fact Sheets: Prostate [Internet]. Available from: http://seer.cancer.gov/statfacts/html/prost.html.
5. Brandon Bernard, Christopher J Sweeney. Management of Metastatic Hormone–Sensitive Prostate Cancer. Curr Urol Rep. 2015;16:14.
6. Bobby C. Liaw, Jeffrey Shevach, William K. Oh. Systemic Therapy for the Treatment of Hormone–Sensitive Metastatic Prostate Cancer: from Intermittent Androgen Deprivation Therapy to Chemotherapy. Curr Urol Rep. 2015;16:13.
7. Loana B. Valenca, Christopher J. Sweeney, Mark M. Pomerantz. Sequencing current therapies in the treatment of metastatic prostate cancer. Cancer Treatment Reviews. 2015;41:332–40.
8. Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben–Josef E, Mendelson DS, et al. Initial hormonal management of androgen–sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2007;25(12):1596–605.
9. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration–resistant prostate cancer. Eur Urol. 2014;65(2):467–79.
10. Mohler JL, Kantoff PW, Armstrong AJ, Bahnson RR, Cohen M, D'Amico AV, et al. Prostate cancer, version 2.2014. National Comprehensive Cancer Network. J Natl Compr Canc Netw. 2014;12(5):686–718.
11. Bernard B, Sweeney CJ. Management of metastatic hormone–sensitive prostate cancer. Curr Urol Rep. 2015;16(3):14.
12. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Lancet. 2000;355(9214):1491–8.
13. Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev. 2000;(2):CD001526.
14. Samson DJ, Seidenfeld J, Schmitt B, Hasselblad V, Albertsen PC, Bennett CL, et al. Systematic review and meta–analysis of monotherapy compared with combined androgen blockade for subjects with advanced prostate carcinoma. Cancer. 2002;95(2):361–76.
15. Vis AN, Schroder FH. Key targets of hormonal treatment of prostate cancer. Part1: the androgen receptor and steroidogenic pathways. BJU Int 2009;104:438–48.
16. Kirby M, Hirst C, Crawford ED. Characterising the castration–resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180–92.
17. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration resistant prostate cancer

progressing after docetaxel treatment: a randomized open–label trial. Lancet. 2010;376:1147–54.
18. Karim Fizazi, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, Fred Saad, Paul Mainwaring, Stephen Harland, Oscar B Goodman Jr, Cora N Sternberg, Jin Hui Li, Thian Kheoh, Christopher M Haqq, Johann S de Bono, for the COU–AA–301 Investigators. Abiraterone acetate for treatment of metastatic castration–resistant prostate cancer: final overall survival analysis of the COU–AA–301 randomized, double–blind, placebo–controlled phase 3 study. Lancet Oncol. 2012;13:983–92.
19. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138–48.
20. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187–97.
21. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424–33.
22. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel–T immunotherapy for castration–resistant prostate cancer. N Engl J Med. 2010;363:411–22.
23. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, et al. Alpha Emitter Radium–223 and Survival in Metastatic Prostate Cancer. N Engl J Med. 2013:369(3):213–23.
24. Voskoboynik M, Staffurth J, Malik Z, Sweeney C, Chowdhury S. Charting a new course for prostate cancer' – currying favor for docetaxel in hormone–sensitive metastatic prostate cancer. Expert Rev Anticancer Ther. 2014;14(11):1253–6.
25. Sweeney, JCO 2014; 32. Abstract LBA2.
26. James ND, Spears MR, Clarke NW et al. Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel era": data from 917 subjects in the control arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). European Urology. 2015;67(6):1028–38.
27. Docetaxel and/or zoledronic acid for hormone–naïve prostate cancer: First overall survival results from STAMPEDE (NCT00268476). J Clin Oncol. 2015;33 suppl:abstr 5001.
28. Cella D, Rosenbloom SK, Beaumont JL, Yount SE, Paul D, Hampton D, et al. Development and Validation of Eleven Symptom Indexes to Evaluate Response to Chemotherapy for Advanced Cancer. J Natl Compr Canc Netw. 2011;9(3):268–78.
29. Cleeland CS. The Brief Pain Inventory User Guide [Internet] 2009. Available from: www.mdanderson.org.
30. Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for subjects with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26:1148–59.
31. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.

32. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration–Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402–18.
33. Parker C, Gillessen S, Heidenreich A, Horwich A, on behalf of the ESMO Guidelines Committee. Annals of Oncology 26 (Supplement 5): v69–v77, 2015.
34. Lolli C, De Lisi D, Conteduca V, Gurioli G, Scarpi E, Schepisi G, et al. Testosterone levels and androgen receptor copy number variations in castration-resistant prostate cancer treated with abiraterone or enzalutamide. Prostate. 2019;79(11):1211–1220.

15. Protocol amendments

15.1 Amendment 2

Amendment 2 is a global amendment dated 04 OCT 2016.

15.1.1 Overview of changes to the study

15.1.1.1 Modification 1: New drug–drug interaction data available

It was clarified that interaction between ODM–201 and P–gp or BCRP are expected *in vivo* based on *in vitro* data and preliminary clinical study results. Text in the protocol was revised, to mention the preliminary results of a drug–drug interaction clinical study, and to provide the Investigators with suggestions how to manage relevant concomitant medications.

Rationale: based on newly available information from a drug–drug interaction clinical study and following IB revision, the protocol text has been revised and aligned.

Sections affected by this modification: 3.2.2 Nonclinical pharmacokinetics and metabolism, 3.2.4 Drug–drug interactions, 3.2.5 Clinical studies with ODM–201, 8.1.2 Permissible concomitant medications and treatments.

15.1.1.2 Modification 2: Clarification of PK analysis

Wording defining the patient population for the detailed PK analysis was revised and clarified throughout the protocol. Wording about docetaxel analysis for the sparse PK sampling in all randomized subjects was also revised and clarified throughout the protocol.

Rationale: Modification was done to clarify that the patients participating to the detailed PK analysis must have received at least one cycle of docetaxel, and to clarify the timing of the sparse PK sampling as well as the additional analysis of docetaxel in all the randomized subjects.

Sections affected by this modification: 3.2.4 Drug–drug interactions, 3.3 Rationale of the study, 5 Study design, 7.1 Treatments to be administered, 7.5 Blinding, 9.1 Tabular schedule of evaluations, 9.2.2.1 Day 1 (Visit 1), 9.5.1 Drug measurements, 9.5.2 Pharmacokinetic evaluation, 10.2 Analysis sets, 10.3.5 Pharmacokinetics, 13.1.1 Independent data monitoring committee.

15.1.1.3 Modification 3: Addition of non–protein–bound (free) testosterone analysis

Wording throughout the protocol was revised to add the non–protein–bound (free) testosterone analysis in a subset of 300 subjects.

Rationale: Low testosterone levels are expected in subjects during ADT treatment, therefore the sex hormone–binding globulin and albumin concentrations will be determined to calculate the non–protein–bound (free) testosterone in a subset of approximately 300 patients. Non-protein–bound (free) testosterone analysis results will be compared to the results from the calculation. In case non–protein–bound (free) testosterone is not measurable in all the subjects of that subset of approximately 300 patients, the calculation will be used.

Sections affected by this modification: 9.1 Tabular schedule of evaluations, 9.2.1 Screening period, 9.2.2.2 Visit 2 and subsequent visits (every 12 weeks ± 7 days), 9.2.3 Active Follow-up period, 9.6.3.1 Laboratory safety assessments

15.1.1.4 Modification 4: Administrative changes

Sponsor's study medical expert was updated due to a change in sponsor's personnel. The contact information was also added to Section 13.1 as per template. The contact details of Co-ordinating investigators were also added.

Sections affected by this modification: Title page, 13.1 Investigator(s) and other study personnel.

15.1.1.5 Modification 5: Other clarifications and corrections

- Scheme of study periods was updated: "treatment with study drug" was changed to "treatment period" to clarify that also docetaxel is given during treatment period.
- Subheading "Further safety" was added as per template, content was not changed.

Sections affected by this modification: 5 Study design, 9.6.3 Further safety

15.1.2 Changes to the protocol text

Changes to the protocol text done in Amendment 2 are provided in Section 15.1.2 of Amendment 2.

15.2 Amendment 5

Amendment 5 is a global amendment dated 12 FEB 2018.

15.2.1 Overview of changes to the study

15.2.1.1 Modification 1: New drug-drug interaction data available

Text was modified to include the results of drug–drug interaction clinical study, and to provide the Investigators with guidance how to manage relevant concomitant medications: Concomitant treatment with strong and moderate CYP3A4 inducers should be avoided. The list of strong and moderate CYP3A4 inducers was also included as an appendix.

Rationale: Based on clinical study results (Study 17726), strong CYP3A4 and P-gp inhibitors and strong CYP3A4 inducers affect the PK of darolutamide. Results indicate that co-administration of darolutamide with a strong CYP3A4 or P-gp inhibitor does not result in a clinically relevant increase of darolutamide plasma concentrations. Results also indicate that repeated co-administration of strong or moderate CYP3A4 inducers with darolutamide is expected to reduce darolutamide plasma concentrations. Therefore, concomitant intake of strong or moderate CYP3A4 inducers should be avoided.

Sections affected by this modification: List of abbreviations, 3.2.4 Drug-drug interactions, 8.1.2 Permissible concomitant medications and treatments, 16.5 List of strong and moderate CYP3A4 inducers (*new appendix added*)

15.2.1.2 Modification 2: Modification of the dosing language

The wording for the study drug dose to be administered was modified and harmonized throughout the protocol: 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.

A guidance text in the event of a missed dose was added: if a dose of study drug is delayed, dose can be taken up to 6 hours to make up for the missed one.

Rationale: The change was done to align darolutamide dosing wording across the development program. In addition, instructions for handling a missed dose were missing from the protocol.

Sections affected by this modification: 2 Synopsis, 5 Study design, 7.1 Treatments to be administered, 7.4.1 Dose modifications of study drug

15.2.1.3 Modification 3: Clarification of docetaxel dosage and administration

The possibility to administer docetaxel as per local practice (if different from the regimen described in the summary of product characteristics) was removed from the protocol, and also the guidance to refer to the local prescribing information was deleted. Docetaxel should be administered at 75 mg/m^2 as 1 hour IV infusion every 3 weeks for 6 cycles. Infusions longer than 1 hour are acceptable for medical reasons at Investigator's discretion. It was also clarified that the first cycle of docetaxel should be administered within 6 weeks after start of study drug instead of 6 weeks after randomization. Rationale for pre–medication instructions was also clarified.

Rationale: The change was done to clarify that pre–medication, docetaxel dose and infusion schedule must be in accordance with the label and that docetaxel can only be administered after the patient has started study drug.

Sections affected by this modification: 7.1 Treatments to be administered, 7.4.2 Dosage and administration for background treatment, 7.4.3 Dose modifications of docetaxel background treatment 9.1 Tabular schedule of evaluations, 9.2.2.1 Day 1 (Visit 1)

15.2.1.4 Modification 4: Guidance on laboratory tests before each docetaxel cycle

The list of laboratory assessments that should be performed before each docetaxel cycle was added to the protocol. It was also clarified that docetaxel can only be infused after routine hematology and biochemistry laboratory tests have been obtained and that the results must be reported in the unscheduled hematology and biochemistry eCRF.

Rationale: The modification was done to give further guidance on laboratory safety assessments and to be in line with docetaxel label requirements.

Sections affected by this modification: 7.4.3 Dose modifications of docetaxel background treatment, 9.1 Tabular schedule of evaluations, 9.2.2.1 Day 1 (Visit 1), 9.2.5 Unscheduled visits, 9.6.3.1 Laboratory safety assessments

15.2.1.5 Modification 5: Clarification related to soft tissue/visceral lesions

It was clarified that the evaluation of soft tissue and visceral lesions is done with the same radiological methods and assessed by RECIST criteria.

Rationale: The change was done for clarity and for consistency throughout the protocol.

Sections affected by this modification: 9.2.2.3 Requirement for chest, abdomen and pelvic CT/MRI and bone scan during the study treatment period, 10.3.2 Secondary efficacy variables

15.2.1.6 Modification 6: Time windows for randomization and Visit 1

Protocol was modified to state that randomization must occur within 28 days from ICF signature and that the patient will be randomized at the end of the screening period. In addition, the time window for Day 1 (Visit 1) procedures was adjusted to clarify that procedures scheduled for Visit 1 can occur +3 days after randomization instead of ±3 days.

The modification was done for clarification.

Sections affected by this modification: 9.1 Tabular schedule of evaluations, 9.2 Visit description, 9.2.1 Screening period, 9.2.2.1 Day 1 (Visit 1), 9.5.1 Drug measurements

15.2.1.7 Modification 7: Switch of ADT to LHRH agonist prohibited

ADT switch to LHRH agonist was added to the list of prohibited concomitant medications and treatments. It was also clarified that ADT switch to an antagonist is allowed during study treatment.

Rationale: Switch of ADT to LHRH agonist may cause flare reactions, impacting subject's safety and radiological assessments, therefore it is prohibited. Opposite a switch to an LHRH antagonist is permitted.

Sections affected by this modification: 8.1.2 Permissible concomitant medications and treatments, 8.1.3 Prohibited concomitant medications and treatments

15.2.1.8 Modification 8: Collection of whole blood sample for pharmacogenetics test allowed at other visits if missed at Visit 1

A whole blood sample for pharmacogenetic testing will be collected preferably at Visit 1 from subjects who have signed pharmacogenetic consent. However, the protocol was modified to allow the collection at any other visit during the treatment period if missed at Visit 1

Rationale: To ensure completeness of sample collection for pharmacogenetics, more flexibility was added to the timing of collecting the respective blood samples.

Sections affected by this modification: 9.1 Tabular schedule of evaluations, 9.2.2.2 Visit 2 and subsequent visits (every 12 weeks ± 7 days), 9.7.1.4 Genetic biomarker analysis from whole blood

15.2.1.9 Modification 9: Unblinding in non-emergency situations not permitted

It was clarified that progressive disease does not routinely constitute an emergency situation, therefore unblinding the label only for subsequent treatment decision is not allowed.

Rationale: The modification was done to clarify that unblinding in non-emergency situations is not permitted.

Sections affected by this modification: 7.5 Blinding

15.2.1.10 Modification 10: Clarification of PK sampling

It was clarified that two additional blood samples for sparse PK analysis can be taken from docetaxel cycle 1 onwards from patients who do not belong to the dense PK subset.

Rationale: To provide clear instructions to the sites regarding collection of blood samples for sparse PK analysis.

Sections affected by this modification: 9.1 Tabular schedule of evaluations, 9.5.1 Drug measurements

15.2.1.11 Modification 11: Clarification of laboratory safety assessments

It was clarified in the protocol text that PSA at screening can be taken within 28 days before randomization.

Rationale: To provide clear instructions about timing of the safety laboratory assessments in the screening period.

Section affected by this modification: 9.6.3.1 Laboratory safety assessments

15.2.1.12 Modification 12: Nomenclature change

With the approval of the INN darolutamide, the Orion drug nomenclature (ODM-201) was replaced with darolutamide throughout the protocol. In addition, the Orion codes for darolutamide diastereomers and metabolite were replaced with trivial names in the entire document as shown in the table under "definitions of terms".

Sections affected by this modification: Definition of terms (*new section added*), the entire document (amended sections are not indicated in the protocol body)

15.2.1.13 Modification 13: Personnel change

The sponsor's medically responsible person was changed as a result of personnel change.

Section affected by this modification: Signature of the sponsor's medically responsible person

15.2.1.14 Modification 14: Other clarifications and corrections

- A typo was corrected in Section 9.7.1.4 (incomplete sentence).
- The abbreviation for AUC(0-x) was corrected in the list of abbreviations.
- The word "approval" was changed to "agreement" in Section 9.2.1 to clarify that the Bayer–designated medical representative provides written agreement to each subject's eligibility. The modification was done to harmonize the language with other study documents.
- The wording related to medical resource use was harmonized ("resource utilization" was changed to "medical resource use") for consistency.
- The statement "not part of this protocol" was removed from the language related to source document checklist to avoid confusion.

Section affected by this modification: List of abbreviations, 9.2.1 Screening period, 9.2.3 Active Follow-up period, 9.7.1.4 Genetic biomarker analysis from whole blood, 9.7.2 Medical resource use, 11.1 Data recording

15.2.2 Changes to the protocol text

Changes to the protocol text done in Amendment 5 are provided in a separate track changes version.

15.3 Amendment 6

Amendment 6 is a global amendment dated 10 DEC 2019.

15.3.1 Overview of changes to the study

Section(s)	Description of change	Rationale
2 Synopsis 8.2 Post-study therapy 9.1 Tabular schedule of evaluations 9.2.2.2 Visit 2 and subsequent visits (every 12 weeks ± 7 days) 9.2.3 Active Follow-up period 9.2.4 Long–term (survival) Follow–up period	The option to continue darolutamide treatment in a separate program was added for those subjects who are ongoing on darolutamide treatment at the time of the primary analysis of the current study. Subjects receiving placebo will discontinue the treatment and complete the study.	To enable subjects who are receiving darolutamide treatment in the current study to continue to receive darolutamide treatment when the study is completed. Subjects in the placebo arm have received standard of care with 6 cycles docetaxel after randomization. Upon disease progression, it will be at the Investigator's discretion to decide on further treatment in the best interest of the patient.
2 Synopsis 5 Study design 9.1 Tabular schedule of evaluations 9.2.5 Unscheduled visits	Additional survival sweeps were added to be performed in all subjects considered alive at the database cut-off date for the second interim analysis and prior to any subsequent additional analysis.	To ensure that survival data is current.
3.2.4 Drug-drug interactions	Detailed information on darolutamide drug-drug interactions were removed and a reference to the latest available version of darolutamide IB was provided instead. The section was updated to reflect that the data from the present study did not reveal any significant impact of darolutamide on the PK of docetaxel.	The most up to date data on drug-drug interactions can be found from the darolutamide IB. The information on the effect of darolutamide on the PK of docetaxel was updated based on the availability of blinded results and the DMC assessment.
8.1.2 Permissible concomitant medications and treatments 16.5 List of strong CYP3A4 inducers	a) The guidance to use strong inhibitors of P-gp and BCRP with caution was removed. b) The guidance to use medicinal products that are sensitive substrates for P-gp or BCRP with caution when co-administered with darolutamide was removed.	a) The results of study 17726 with itraconazole, a strong CYP3A4, P-gp and BCRP inhibitor, did not indicate a clinically relevant impact on the PK of darolutamide. b) Based on the results of study 18860 using dabigatran etexilate as a sensitive P-gp substrate, there is no effect of darolutamide on P-gp

	c) The guidance to monitor subjects receiving concomitant drugs which are mainly metabolized via CYP3A4 enzyme for signs of decreased efficacy was removed. d) The recommendation to avoid concomitant use of moderate CYP3A4 inducers was removed (while strong CYP3A4 inducers should still be avoided). e) The guidance to closely monitor patients for signs and symptoms of increased exposure was updated to include also OATP1B1 and OATP1B3 substrates.	transporter. The effect of darolutamide on BCRP is described in detail based on study 17723 with rosuvastatin. c) Based on the results of study 18860 using midazolam as a sensitive CYP3A4 substrate, darolutamide has only a minor inducing effect on CYP3A4 which is not considered to be clinically relevant. d) Recent results have established the darolutamide exposure-response relationship which showed a flat relationship (maximum PSA response) over the entire exposure range of 600 mg bid and also at exposures below that range. Thus, even with a darolutamide exposure decrease of 50% (driven by a CYP3A4 inducer), there would still be a strong effect on PSA. Therefore, the modification allows the use of moderate CYP3A4 inducers. e) New *in vitro* data on OATP1B1 and OATP1B3 indicated that the effect of darolutamide on such substrates may be clinically relevant.
9.6.1.3 Assessments and documentation of adverse events	The guidance on AE reporting was modified to clarify that disease progression should not be reported as an AE. Instead, the associated signs and symptoms should be recorded as AEs.	The change was done for clarification.
9.1 Tabular schedule of evaluations 9.2.1 Screening period 9.2.2.2 Visit 2 and subsequent visits (every 12 weeks ± 7 days) 9.2.3 Active Follow-up period 9.6.3.1 Laboratory safety assessments	In a subset of subjects, additional determination of total and free testosterone was added to be performed also at the EOT Visit	Emerging scientific data suggest that investigating free testosterone at the time of disease progression (which likely will lead to stopping study treatment) will be worth analyzing in relation to the efficacy endpoints (34)
9.8 Appropriateness of procedures /	Clarifications and corrections	Modifications were done for clarification

measurements 10.3.2 Secondary efficacy variables 10.3.4 Other exploratory variables	were done: • MedDRA version number removed • “Analgesic use” changed to “opioid use” • Definition of “time to PSA progression” clarified • Typos corrected	and consistency.
Title page Signature of the sponsor’s medically responsible person 13.1 Investigator and other study personnel	Sponsor’s medical expert and medically responsible person were changed.	Administrative changes.
15.1.2 Changes to the protocol text	The detailed old vs. new text comparison for protocol amendment 2 was replaced with a reference to the respective protocol amendment.	To improve readability, and to reduce complexity of the protocol.

15.3.2 Changes to the protocol text

Changes to the protocol text done in Amendment 6 are provided in a separate track changes version.

15.4 Amendment 7

Amendment 7 is a global amendment dated 26 MAY 2020.

15.4.1 Overview of changes to the study

Section(s)	Description of change	Rationale
1 Title page	New e-signature text added.	New e-signature process implemented at Bayer.
2 Synopsis 5 Study design 9.1 Tabular schedule of evaluations (footnote v) 9.2.5 Unscheduled visits 10.3.1 Primary efficacy variable 10.5 Planned interim analyses 13.1.1 Independent data monitoring committee	Planned second interim analysis will not be performed.	Due to the implications of the COVID-19 pandemic on the conduct of study procedures and data collection at the study sites, the risk for not achieving the needed quality of data for a formal analysis is considered to be too high. Therefore, the second interim analysis, which was expected to be conducted in the second half of 2020, will not be performed. As a consequence, there is no splitting of alpha for efficacy between the now dropped second interim analysis and the final analysis. This change does not affect the regular DMC for safety.
9.7.1 Biomarker investigations	Clarification added for biomarker analysis and reporting.	To allow for inclusion of biomarker analysis in the main study SAP and to be consistent with other parts of the protocol.
10.3.2 Secondary efficacy variables	Added text regarding ranking of secondary endpoints.	To clarify that type 1 error control will include the ranking of secondary endpoints.
10.5 Planned interim analyses	Stopping boundaries for the futility interim and final analyses together will use a beta-spending function based on the actual number of events.	Due to removal of interim analysis 2, the sentence regarding alpha-spending has been removed. Added a statement about beta-spending for clarification.

15.4.2 Changes to the protocol text

Changes to the protocol text done in Amendment 7 are provided in a separate track changes version.

16. Appendices

16.1 Eastern Cooperative Oncology Group performance status

Grade	Description
0	Fully active, able to carry on all pre–disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self–care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self–care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self–care. Totally confined to bed or chair.
5	Death

16.2 National Cancer Institute–Common Terminology Criteria for Adverse Events

This study will utilize the NCI–CTC for Adverse Events Version 4.03 for toxicity and serious AEs reporting. A copy of the CTC Version 4.03 can be downloaded in PDF form from http://evs.nci.hin.gov/ftp1/CTCAE/About.html.

All appropriate treatment areas should have access to a copy of the NCI–CTC Version 4.03.

16.3 NCCN–FACT FPSI–17

Below is a list of statements that other people with your illness have said are important.
Please circle or mark one number per line to indicate your response as it applies to <u>the past 7 days.</u>

			Not at all	A little bit	Some what	Quite a bit	Very much
DRS–P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	P7	I have difficulty urinating	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	NCCN3	I have weakness in my legs	0	1	2	3	4
	P3	My pain keeps me from doing things I want to do	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS–E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	P6	I have trouble moving my bowels	0	1	2	3	4
TSE	GS7	I am satisfied with my sex life	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS–P=Disease–Related Symptoms Subscale – Physical
DRS–E=Disease–Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well–Being Subscale
English (Universal), Copyright 2001 03 March 2010

16.4 BPI–SF

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

Items 1 and 2 removed with permission of copyright owner

3.	Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.										
	0 No Pain	1	2	3	4	5	6	7	8	9	10 Pain as bad as you can imagine
4.	Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.										
	0 No Pain	1	2	3	4	5	6	7	8	9	10 Pain as bad as you can imagine
5.	Please rate your pain by circling the one number that best describes your pain on the average.										
	0 No Pain	1	2	3	4	5	6	7	8	9	10 Pain as bad as you can imagine
6.	Please rate your pain by circling the one number that tells how much pain you have right now.										
	0 No Pain	1	2	3	4	5	6	7	8	9	10 Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

[redacted] ___/___/____ [redacted] _____

_____ _____ _____

Last First Middle Initial

Items 7 and 8 removed with permission of copyright owner

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

16.5 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