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Official Title:	A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC)
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Title Page

Protocol Title: A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC)

Protocol Number: 21140 Clinical Study Protocol

Amendment Number: Amendment 1 (Global)

Protocol Version: 2.0

Compound: Darolutamide (BAY 1841788)

Study Phase: 3

Short Title: Phase 3 study of darolutamide in addition to ADT versus placebo plus ADT in men with mHSPC

Acronym: ARANOTE

Sponsor Name and Legal Registered Address:

Sponsor (Non-US):

Bayer Consumer Care AG, Peter-Merian-Strasse 84, 4052 Basel, Switzerland

Sponsor (US territory):

Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA

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Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 1 (Global)	2.0	28 JUN 2022	
Local Amendment (Canada) CAN-1	CAN-1	22 DEC 2020	
Original Clinical Study Protocol	1.0	24 SEP 2020	No versioning applied to the original protocol as per company convention at the time of protocol generation. The original protocol is technically considered as document version 1.0.

Protocol Amendment Summary of Changes Table

Overall Rationale for the Amendment:

The rationale for Amendment 1 was to add the open-label phase to the study design and to update the sample size. In addition, text was added to provide guidance on criteria for study drug discontinuation in the event of suspected drug-induced liver injury (DILI). Changes were also added to the other pre-specified endpoints for clarification, as well as a new endpoint added for time to first prostate cancer-related invasive procedure. Futility Interim Analysis was removed.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema (Figure 1-1 Study Design) 1.3 Schedule of Activities (SoA) 4.1 Overall Design 4.1.1 Screening Period 4.1.2 Treatment Period 4.1.3 Active Follow-up Period 4.1.4 Long-term (survival) Follow-up Period 4.2 Scientific Rationale for Study Design 4.4 End of Study Definition 7.1 Discontinuation of Study Intervention	Added open-label phase to the study design. New guidance on the management of radiological scans and study periods. Added new Table 1-3: Schedule of Activities for open-label phase.	To grant patients access to the active drug, in case of positive results at the primary completion. Therefore, text was modified in these sections. New guidance on the management of radiological scans and study periods entered to decrease the risk of data loss for the primary and key secondary endpoints.

Section # and Name	Description of Change	Brief Rationale
8.1 Efficacy Assessments 9.4.2.2 Secondary Endpoints 9.6 Data Monitoring Committee (DMC) or other Review Board		
1.1 Synopsis (Overall Design: Number of Participants:) 1.2 Schema (Figure 1-1 Study Design) 4.1 Overall Design 4.2 Scientific Rationale for Study Design 9.2 Sample Size Determination	Updated increased sample size numbers.	Compared to the original protocol version, a higher dropout rate is expected, mainly due to unpredictable geopolitical situation in some participating countries. Therefore, sample size has been updated.
2.3.1 Risk Assessment 6.6.3 General Requirements for Dose Modifications of Study Drug 7.1 Discontinuation of Study Intervention 10.4 Appendix 4: Participant Discontinuation 11. References	Addition of newly identified safety data for darolutamide. Text added to provide guidance on criteria for study drug discontinuation in the event of suspected drug-induced liver injury (DILI). Note: numbering change as Appendix 4 was newly added. New reference (FDA, 2009) was added.	Newly identified safety data across darolutamide clinical trials, including cases of idiosyncratic hepatic reactions that were reversible upon treatment discontinuation.
3. Objectives and Endpoints 3. Objectives and Endpoints (Table 3-1: Objectives and Endpoints) 4.1.3 Active Follow-up	Added text clarifying that all objectives listed in Table 3-1 will be analyzed at the primary completion, and only limited analyses will be conducted in the final analysis. Added patient relevant objective and endpoint/text to other pre-specified objectives and endpoints	For alignment and clarification.

Section # and Name	Description of Change	Brief Rationale
Period 4.1.4 Long-term (survival) Follow-up Period 8.1 Efficacy Assessments 9.4.2.2 Secondary Endpoints 9.4.2.3 Other Pre-specified Endpoints	(which are reflected throughout the listed sections).	
9.6 Data Monitoring Committee (DMC) or other Review Board	Removed futility analysis.	Futility analysis considered not needed in light of additional data from study 17777 (ARASENS), where darolutamide demonstrated benefit in mHSPC setting.
3. Objectives and Endpoints (Table 3-1) 9.4.2.3 Other Pre-specified Endpoints	Removed "radiological" from radiological progression-free survival 2 (rPFS2).	For alignment and clarification.
6.3.2 Emergency unblinding by the Investigator	Removed text referring to "Emergency" unblinding in heading and section. Further, added text that unblinding may also be performed after participant discontinues from the treatment phase.	To allow unblinding for subsequent anti-cancer treatment choice under specific circumstances.
8.4 Treatment of Overdose	Removed PK analysis text as PK parameters are not evaluated in this study.	Clarification.
1.1 Synopsis 4.1 Overall Design 5.1 Inclusion Criteria (criterion #5) 5.2 Exclusion Criteria (criterion #3) 6.1 Study Interventions Administered	Updated background treatment start time wording ("not earlier than 12 weeks") for consistency.	To harmonize.
5.1 Inclusion Criteria (criterion #4)	Added a note to clarify participants with bone scan showing a diffuse, intense,	For clarification.

Section # and Name	Description of Change	Brief Rationale
	skeletal uptake of the tracer with absent renal and background activity are considered ineligible.	
5.1 Inclusion Criteria (criterion #10) 8.3.5 Pregnancy	Modified wording for clarity.	For clarification.
5.2 Exclusion Criteria (criterion #3)	Added two new bullet points to criterion #3.	For clarity.
6.5.2 Prohibited Concomitant Therapy	Added new bullet point ("Any other anti-cancer treatment for prostate cancer, excluding local therapies and ADT").	Use of other treatments with anti-cancer effect may bias efficacy and safety endpoints; therefore, they are considered prohibited concomitant treatments.
1.3 Schedule of Activities (SoA) Table 1-2 Schedule of Activities for double-blind period	Modified and updated Table 1-2 footnotes c, i, k, m, n, q, v, and x. Added prostate cancer related invasive procedure with respective footnote y.	For clarity and correction.
2.1 Study Rationale	Removed text to clarify where the study is planned to be conducted.	For clarity.
2.1 Study Rationale 2.3 Benefit/Risk Assessment 2.3.1 Risk Assessment 2.3.2 Benefit Assessment 2.3.3 Overall Benefit: Risk Conclusion	Added study 17777 (ARASENS) data.	New efficacy and safety data are available for darolutamide in mHSPC setting.
3. Objectives and Endpoints (Table 3-1) 8.8.1 Potential Predictive Biomarkers 8.8.2 Pharmacodynamic Biomarkers	Removed footnote ** from Table 3-1, which was referring to biomarker analyses text for China. Updated biomarker analyses text for China.	Clarification of the strategy for biomarker analysis.

Section # and Name	Description of Change	Brief Rationale
9.4.2.3 Other Pre-specified Endpoints		
5.1 Inclusion Criteria (criteria #9 and #11) 6.6.3 General Requirements for Dose Modifications of Study Drug 11. References	For Canada sites: Added wording to criterion #9 indicating screening values for ALT, AST and total bilirubin. In addition, criterion #11 was added with eGFR values at screening. Added text recommending dose adjustment for participants experiencing decreased to severe renal impairment. Reference for the eGFR formula was added.	Health Authority for Canada request.
5.2 Exclusion Criteria	Removed radiopharmaceuticals from criterion #4 and added it to criterion #3. Further added use of any anti-cancer treatments as exclusion criterion.	Previous use of radiopharmaceuticals or any other treatments with anti-cancer effect may bias efficacy and safety endpoints; therefore, they are considered prohibited prior treatments.
6.5.1 Permitted Concomitant Therapy	Added text permitting vaccines for COVID-19 and flu during study treatment.	For clarity.
6.5.2 Prohibited Concomitant Therapy	Added text not permitting “use of live, attenuated, replication-competent vaccines”.	For clarity.
6.1 Study Interventions Administered 6.5.1 Permitted Concomitant Therapy 9.2 Sample Size Determination	Removed text.	Redundant.
6.1 Study Interventions Administered	Removed documented radiological disease progression assessed by	For clarity.

Section # and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention	central review.	
6.2 Preparation/Handling/ Storage/Accountability 6.4 Study Intervention Compliance	Removed IWRS text.	Correction.
7.1.2 Rechallenge	Removed first sentence in last paragraph.	Correction.
8.1 Efficacy Assessments	Added paper forms for administered questionnaires (in second to last paragraph of this section).	To allow the use of paper forms in absence of the ePRO devices.
4.1.4 Long-term (survival) Follow-up Period 7.1 Discontinuation of Study Intervention 8.2.3 Electrocardiogram (ECG) 9.4 Statistical Analyses 9.4.2.1 Primary Endpoint 9.4.3 Safety Analyses	Changes were added for clarity: • indicating double-blind and/or open-label study phase • describing QTc intervals will be calculated by eCRF system	Modifications were made for clarity and completeness.
9.4.3 Safety Analyses	Removed "(+7 days)" from safety assessment period for TEAE starting after the first dose of study drug until 30 days after the last treatment with darolutamide/placebo.	Correction.
3. Objectives and Endpoints (Table 3-1) 4.1.2 Treatment Period 4.1.3 Active Follow-up Period 4.1.4 Long-term (survival) Follow-up Period 5.4 Screen Failures 6.5.1 Permitted Concomitant Therapy 6.6.3 General Requirements for Dose Modifications of Study	Minor text modifications.	For clarity and correction.

Section # and Name	Description of Change	Brief Rationale
Drug (Table 6-3: Study drug dose modifications) 9.4.2.2 Secondary Endpoints 9.4.2.3 Other Pre-specified Endpoints		
10.11 Appendix 11: Abbreviations	Made updates and corrections.	For completeness.
2.3 Benefit/Risk Assessment 11. References	Added reference in Section 2.3 (Smith et al. 2022).	Update.
1.1 Synopsis (Secondary objectives) 1.2 Schema (Figure 1-1 Study Design) 1.3 Schedule of Activities (SoA, Table 1-2) 3. Objectives and Endpoints (Secondary and other pre-specified objectives) 4.1.3 Active Follow–up Period 4.1.4 Long–term (survival) Follow–up Period 5.2 Exclusion Criteria 6.5 Concomitant Therapy 6.5.2 Prohibited Concomitant Therapy 7.1 Discontinuation of Study Intervention 8.1 Efficacy Assessments 9.4.2.2 Secondary Endpoints	Terminology changed from “antineoplastic” to “anti-cancer” at all occurrences.	For consistency.
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized.

A tracked changes version of the document will be provided separately.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A randomized, double-blind, placebo-controlled Phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC)

Short Title: Phase 3 study of darolutamide in addition to ADT versus placebo plus ADT in men with mHSPC

Rationale:

For decades, the treatment of mHSPC was ADT; however, resistance ultimately occurs, and patients progress to metastatic castration-resistant prostate cancer (mCRPC) from which they eventually die (Shevach et al. 2019).

Pivotal trials confirmed that adding docetaxel, abiraterone acetate, enzalutamide or apalutamide to ADT result in improvement of overall survival (OS) and/or radiological progression-free survival (rPFS) for patients with mHSPC (Di Nunno et al. 2020). Despite the efficacy benefits reported with all combinations in mHSPC, the safety profile is an important factor to be considered for treatment acceptance together with patients' comorbidities who require chronic treatments (Cattrini et al. 2019).

Darolutamide is a potent androgen receptor inhibitor (ARi) with low blood-brain barrier penetration and low potential for drug-drug interactions (Moilanen et al. 2015, Shore et al. 2019, Williams et al. 2020). Considering the unique safety profile of darolutamide, the present study will evaluate darolutamide in addition to ADT in mHSPC patients.

Objectives and Endpoints

The purpose of this study is to evaluate the efficacy and safety of darolutamide in addition to ADT versus placebo plus ADT in participants with mHSPC.

Table 1–1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS in participants with mHSPC	• rPFS assessed by central review based on RECIST v. 1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases
Secondary	
• To evaluate efficacy of darolutamide in addition to ADT compared to placebo plus ADT by improving OS, time to progress to CRPC, time to initiation of subsequent anti-cancer therapy, time to PSA progression, and undetectable PSA rates	• OS – key secondary endpoint • Time to CRPC • Time to initiation of subsequent anti-cancer therapy • Time to PSA progression • PSA undetectable rates (<0.2 ng/mL)
• To estimate the participant's quality of life benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving symptomatic time to pain progression	• Time to pain progression (BPI-SF)
• To assess the safety of darolutamide in addition to ADT compared to placebo plus ADT in participants with mHSPC	• AE assessments using NCI-CTCAE (v.5.0)

Abbreviations: ADT = Androgen Deprivation Therapy; AE = Adverse event; BPI-SF = Brief Pain Inventory-Short Form; CRPC = Castration-resistant prostate cancer; mHSPC = Metastatic hormone-sensitive prostate cancer; NCI-CTCAE = National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0); OS = Overall survival; PCWG3 = Prostate Cancer Working Group 3; PSA = Prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = Radiological progression-free survival

Overall Design:

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

Number of Participants:

Approximately 665 participants who meet the eligibility criteria will be randomly assigned to study drug (darolutamide or placebo), at the ratio of 2:1. All participants who were randomized are included in the Full Analysis Set (FAS). The participants in this set will be grouped according to the treatment they were allocated to receive at randomization, irrespective of actual treatment. Eligibility requirement of metastatic disease by radiologic assessment will be confirmed by central review during screening.

Participants will by stratified at randomization as follows:

- Presence of visceral metastases versus absence of visceral metastases assessed by central review
- Prior local therapy versus no prior local therapy

Intervention Groups and Duration:

In the double-blind period, the study comprises 4 consecutive periods: Screening, Treatment, Active Follow–up, and Long–term (survival) Follow–up. Open-label phase will start in case of positive benefit/risk assessment for darolutamide, based on data from primary analysis.

After an up to 28-day screening period, participants who satisfy all eligibility criteria (see Section 5.1 and Section 5.2) will be randomized in a 2:1 ratio to receive one of the following **study drugs**:

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

Background treatment: All participants must receive ADT of investigator's choice (luteinizing hormone-releasing hormone [LHRH] agonist/antagonists or orchiectomy) as standard therapy, not earlier than 12 weeks before randomization, on a continuous basis.

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

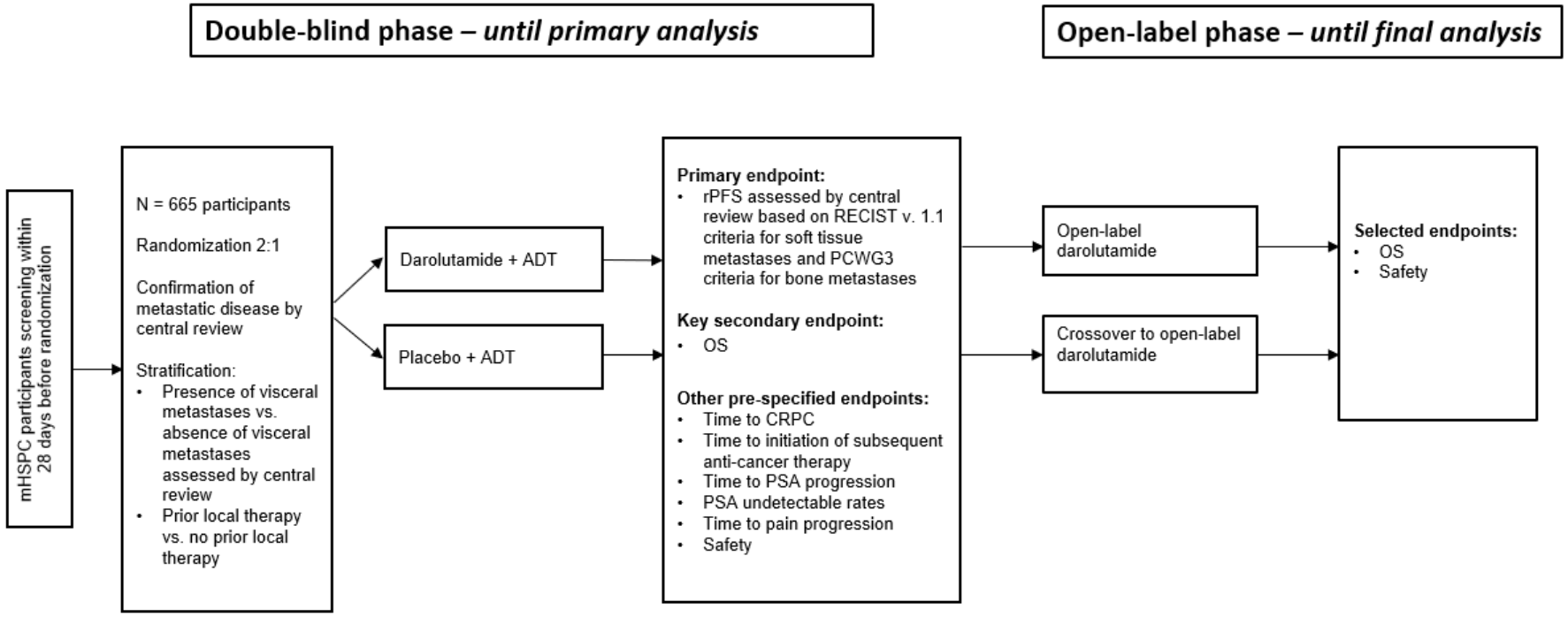
During Treatment period, participants will be evaluated with regular clinic visits for efficacy and safety as described in the SoA (Section 1.3). The dose or dosing schedule of the study drug may be modified following the occurrence of adverse events (AEs) as described in Section 6.6. Participants will receive study drug until documented radiological disease progression assessed by central review, unacceptable toxicity or until any other withdrawal criteria specified in Section 7.1 is met.

After discontinuation of study drug, participants will enter the Active Follow-up period where clinic visits will continue for approximately 1 year (12 ±1 months), and then will be contacted by telephone in the Long-term Follow-up period, unless central imaging and PSA evaluations have to be continued, in which case participants should continue with clinic visits. Please refer to Section 4.1 for further details on study design. Please refer to Section 4.1.4 for further details on the need to continue imaging assessments in the Long-term Follow-up period.

Data Monitoring Committee: Yes

1.2 Schema

Figure 1–1 Study Design



Abbreviations: ADT = Androgen Deprivation Therapy; CRPC = Castration-resistant prostate cancer; mHSPC = Metastatic hormone-sensitive prostate cancer; OS = Overall survival; PCWG3 = Prostate Cancer Working Group 3; PSA = Prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = Radiological progression-free survival; vs. = versus

1.3 Schedule of Activities (SoA)

Table 1–2 Schedule of Activities for double-blind period

Procedures[x]	**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 Every 12 weeks (±7 days)[u]	EOT Visit: 30 days (+7 days) after last dose of study drug[v]	Approximately every 12 weeks from discontinuation of treatment for approximately 1 year (12 ±1 months)	Approximately every 12 weeks after Active Follow–up, until death, lost to follow–up, consent withdrawal, or end–of–study
Signed and dated informed consent	X						
Informed consent for WGS (optional) (not applicable for China)	X						
Demography	X						
Medical history	X						
Prostate cancer history[b]	X						
Eligibility criteria	X	X					
Symptom/QoL by FACT-P questionnaire[c]		X	(X)[d]	X	X	X	
Pain questionnaire BPI–SF[c, e]		X	X	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[f]			X[f]				
Physical examination[g]	X		X[h]	X	X		
12–lead ECG		X	(X)[o]	X	X		
Vital signs (BT, HR, BP)		X	X[h]	X	X		
Laboratory safety assessments (hematology, general chemistry and		X		X	X		

Table 1–2 Schedule of Activities for double-blind period

Procedures[x]	**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 Every 12 weeks (±7 days)[u]	EOT Visit: 30 days (+7 days) after last dose of study drug[v]	Approximately every 12 weeks from discontinuation of treatment for approximately 1 year (12 ±1 months)	Approximately every 12 weeks after Active Follow–up, until death, lost to follow–up, consent withdrawal, or end–of–study
urinalysis)[i]							
Serum PSA[i]	X			X	X	(X)	(X)
Testosterone[i]	X			X	X	(X)	(X)
Biomarker plasma		X		X[j]	X		
Biomarker whole blood for pharmacogenetic analysis (not applicable for China)			X[w]	(X)[o]			
Biomarker tumor tissue (e.g. biopsy) (not applicable for China)	X[k]				X[l]		
ECOG PS	X		X	X	X		
CT/MRI[n]	X[m]			X[n]	X[n]	X[n]	X[n]
Bone scan[n]	X[m]			X[n]	X[n]	X[n]	X[n]
First SSE[p]				X	X	X	
Prostate cancer related invasive procedure[y]			X	X	X	X	X
Post–study anti-cancer therapy[q]						X	X
AEs/SAEs	X	X	X	X	X	X[s]	X[s]
Concomitant treatments[r]	X	X	X	X	X	X[s]	X[s]
Study drug dispensing			X	X			
Survival status[t]						X	X

Abbreviations: ADT = Androgen deprivation therapy; AE = Adverse events; AR = Androgen receptor; BHA = Bone health agents; BP = Blood pressure; BPI–SF = Brief Pain Inventory–Short Form; BT = Body temperature; CNS = Central nervous system; CT = Computed tomography; EBRT = External beam radiation therapy; ECG =

Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = Electronic case report form; EOT = End of treatment; FACT-P = Functional Assessment of Cancer Therapy-Prostate Cancer questionnaire; HR = Heart rate; ICF = Informed consent form; LHRH = Luteinizing hormone releasing hormone; MRI = Magnetic resonance imaging; OS = Overall survival; PI = Principal Investigator; PSA = Prostate–specific antigen; QoL = Quality of life; SAE = Serious adverse event; SSE = Symptomatic skeletal event; WGS = Whole genome sequencing; (X) = (the X in parenthesis) indicates optional assessment.

Participants will receive study drug (darolutamide or placebo) in addition to ongoing ADT (LHRH agonist/antagonist at the investigator discretion; prior therapy with first-generation AR inhibitors given with LHRH agonist must be discontinued within 1 day before study treatment start).

- **a.** The study treatment will be administered until documented radiological disease progression assessed by central review, unacceptable toxicity or until any other withdrawal criteria specified in Section 7.1 is met.
- **b.** Including prior treatments and procedures.
- **c.** Questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities. In screening 7 days prior to randomization: daily record completion (7 copies), 7th day may correspond to Visit 1 Day 1 (V1D1).
- **d.** If not collected at the Screening visit. The (X) indicates optional assessment.
- **e.** Analgesic consumption and pain assessment questionnaires must be collected on the same day.
- **f.** Randomization must occur within 28 days from ICF signature.
- **g.** Physical examination including assessments of the cardiovascular, respiratory, gastrointestinal, neurological, and skin systems; height (at screening only) and weight will also be measured.
- **h.** If not previously done within 7 days prior study treatment start.
- **i.** PSA and testosterone values are to be assessed by a central laboratory during the study treatment period. PSA and testosterone for participants who discontinue the study treatment before radiological progression must be continued to be assessed by central laboratory also in Active Follow-up visits and Long-term Follow-up periods until radiological progression is assessed by central review or change of anti-cancer therapy. Other laboratory assessments are to be performed by local laboratories. The (X) indicates optional assessment.
- **j.** To be performed at Visit 2 only.
- **k.** Provision of archival tumor tissue at Screening is optional if available. Archival tumor tissue (blocks or predefined number of slides) has to be provided, if available and unless precluded by local regulations. All efforts should be undertaken to collect primary or metastatic tumor if biopsies were taken outside the treating hospital. Participants for whom archival tissue is not available or collection from locations outside the treating hospitals may still be eligible to participate in the study. No fresh biopsies are required to participate. Provision of archival tumor tissue is not applicable for China.
- **l.** Tissue sample from a tumor biopsy at progression is highly encouraged to be taken as per investigator's decision, if technically feasible unless precluded by local guidelines (optional collection). Not applicable for China.
- **m.** ^{99m}Tc-phosphonate bone scan, contrast–enhanced chest, abdomen, and pelvic CT or MRI performed within 42 days prior to start of study treatment are acceptable as screening scans if the standard acquisition procedure according to the Imaging Manual and Section 8.1 was followed.
  Baseline CT/MRI and bone scans must first be reviewed by a local qualified site physician (e.g. site radiologist or PI, at the PI's discretion) to confirm presence of metastases before submitting the scans to central review to confirm eligibility and provide stratification group (visceral disease present vs. absent). If the local qualified site physician detects metastases of only local lymph nodes (below aortic bifurcation) or determines that the screening bone scan is a superscan (Section 5.1, inclusion criterion 4), the scans should not be submitted to central review and participants should not be randomized.
- **n.** In addition to planned study visits, tumor assessment imaging, (^{99m}Tc-phosphonate bone scan, chest, abdomen and pelvic CT or MRI) can be performed at any time in case of PSA progression, symptomatic progressive disease, or change of anti-cancer therapy or if considered appropriate in the investigator's judgment; Brain/CNS CT scan or MRI will be performed in case of symptoms as appropriate. Such unscheduled imaging must be sent for central review and radiological progression assessment. Participants who discontinue study drug without radiological disease progression assessed by central review should continue the schedule of imaging assessments until radiological disease progression is assessed by central review or change of anti-cancer therapy. This also applies to participants who enter the Long-term Follow-up. Once the participant experiences radiological progression assessed by central review, imaging will continue to be performed according to local clinical practice. In the active and long-term follow-up periods, if allowed by local regulations, participants without centrally-assessed

radiological disease progression, for whom start of a subsequent anti-cancer therapy is planned before the next follow-up visit/contact, should perform a tumor assessment (contrast enhanced CT/MRI and bone scan) and submit it to the core imaging laboratory for central radiology review. Note that this tumor assessment is not required if the prior tumor assessment was performed within the previous 30 days.

o. Only if missed at Visit 1. The (X) indicates optional assessment.

p. SSE 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.

q. Documentation of post–study anti-cancer therapies must include the start and stop dates of each treatment and reason for treatment changes (PSA progression, clinical progression, radiological progression, toxicity, other).

r. Including bone health agents (BHA) according to local guidelines for participants with risk of bone fracture.

s. Only SAEs that are considered related to study drug or study participation, with concomitant medications used to treat the event. Also, concomitant medications used to treat related AEs that were unresolved at EOT will be captured in Active and Long-term Follow-up.

t. Survival data will be collected through an additional survival sweep. All participants considered alive shortly after the database cut-off date for the primary analysis and prior to any subsequent analysis of OS will be contacted for survival status.

u. Date of visit is to be calculated based on the previous visit date.

v. The EOT visit will be completed before starting a new anti-cancer therapy if it starts sooner than 30 days (+7 days) after the last dose of study drug.

w. This should be collected pre-dose on Visit 1.

x. Some screening visit procedures and Active Follow-up visit procedures may be conducted using eTools where applicable with the exception of CT/MRI and bone scan.

y. Prostate cancer-related invasive procedure is defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g., catheterization of the bladder, percutaneous drainage of hydronephrosis, palliative electro resection of the prostate, etc.). Prostate cancer-related procedure will be collected at every visit/contact until change of anti-cancer therapy.

Table 1–3 Schedule of Activities for open-label phase

Procedures		**Follow–up Period**		
		Active Follow–up Period		**Long–term Follow–up Period**
	Visit 2 and subsequent visits	**EOT Visit**	**Active Follow–up Visits**	
	Week 12 Every 12 weeks (±7 days)	EOT Visit: 30 days (+7 days) after last dose of study drug	Approximately every 12 weeks from discontinuation of treatment for approximately 1 year (12 ±1 months)	Approximately every 12 weeks after Active Follow–up, until death, lost to follow–up, consent withdrawal, or end–of–study
Signed and dated informed consent	X[a]			
12–lead ECG	X	X		
Vital signs (BT, HR, BP)	X	X		
Laboratory safety assessments (hematology, general chemistry and urinalysis)	X	X		
ECOG PS	X	X		
AEs/SAEs	X	X	X[c]	X[c]
Concomitant treatments[b, c]	X	X	X[c]	X[c]
Study drug dispensing	X			
Survival status			X	X

Abbreviations: AEs = Adverse events; BP = Blood pressure; BT = Body temperature; EOT = End of treatment; ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = Heart rate; ICF = Informed consent form; SAEs = Serious adverse events; PSA = Prostate–specific antigen

a. At the moment of unblinding and if participant is eligible to continue the study treatment, participant will be offered to enter the open-label phase. Open-label phase ICF must be signed before any study-related intervention.

b. Including bone health agents (BHA) according to local guidelines for participants with risk of bone fracture.

c. Only SAEs that are considered related to study drug or study participation, with concomitant medications used to treat the event. Also, concomitant medications used to treat related AES that were unresolved at EOT will be captured in Active and Long-term Follow-up.

2. Introduction

2.1 Study Rationale

For decades, the treatment of metastatic hormone sensitive prostate cancer (mHSPC) was androgen deprivation therapy (ADT); however, resistance ultimately occurs, and patients progress to metastatic castration-resistant prostate cancer (mCRPC) from which they eventually die (Shevach et al. 2019). Various approaches have been tested to enhance disease control and to prolong patient's survival by adding docetaxel, abiraterone/prednisone or next generation androgen receptor inhibitors (ARi), enzalutamide and apalutamide to ADT (Kinsey et al. 2020).

Pivotal trials confirmed that adding docetaxel, abiraterone acetate, enzalutamide or apalutamide to ADT in addition to placebo result in improvement of overall survival (OS) and/or radiological progression-free survival (rPFS) for patients with mHSPC (Di Nunno et al. 2020). The placebo plus ADT (ADT alone) as comparator arm in this trial is therefore consistent with other pivotal studies conducted in the same population.

Additionally, based on the ICH E17 guidance, the comparator(s) in a study should be in principle the same in all participating regions. The study is therefore planned to be conducted in Europe, North America (Ex-US), Asia, and Latin America in locations where ADT alone is a standard of care for these patients.

The safety analyses of the pivotal Phase 3 studies 17712 (ARAMIS) in non-metastatic castration-resistant prostate cancer (nmCRPC), and 17777 (ARASENS) in mHSPC in combination with docetaxel, showed that darolutamide combined with ADT treatment was well-tolerated compared to the placebo arm. Also, the overall TEAE profile in the mCRPC phase 1/2 pool was consistent with that observed in ARAMIS study supporting the favorable safety profile of darolutamide.

As patients with mHSPC are generally asymptomatic, more intensive hormonal therapy could negatively affect the quality of life (QoL) of patients treated. It is noteworthy that darolutamide has shown a favorable safety profile, since mHSPC patients are often on treatment for prolonged periods of time.

Despite the efficacy benefits reported with all combinations in mHSPC for treatment decision, physicians should consider the safety profiles including treatment-induced morbidities related to the long treatment exposure of abiraterone acetate, apalutamide, and enzalutamide.

Abiraterone, apalutamide or enzalutamide in addition to ADT were given for long time periods in patients with mHSPC, leading to long-term exposure morbidities. Mineralocorticoid-associated side effects including hypertension, hypokalemia, hyperglycemia, weight gain and hepatic toxicity have been seen with abiraterone treatment. Patients with co-morbidities such as osteoporosis or diabetes mellitus might be at higher risk for a treatment with abiraterone. Higher rates of fatigue, hypertension, fractures and falls were reported with treatment of enzalutamide and for apalutamide AEs such as rash, pruritus, hot flushes and hypothyroidism. In addition, the risk of seizures should be taken into consideration if patients are planned to receive treatment with either enzalutamide or apalutamide (Cattrini et al. 2019, Chi et al. 2019, Davis et al. 2019, Fizazi et al. 2017). Additionally, potential drug-drug interactions of enzalutamide or apalutamide may be challenging in this patient population with co-morbidities where polypharmacy is the norm.

An analysis of real-world prescription, potential drug-drug interactions were noted in up to 85% of patients receiving treatment with enzalutamide for mCRPC (Benoist et al. 2018).

Darolutamide is a potent ARi with low blood-brain barrier penetration and low potential for drug-drug interactions. Preclinical studies of darolutamide have shown a low blood-brain barrier penetration compared to that of available therapies, which may indicate an improved safety profile with respect to CNS related events. Darolutamide also exhibited low potential for drug-drug interaction, allowing a greater flexibility for the use of concomitant medications without compromising therapeutic efficacy or safety of therapy. (Moilanen et al. 2015, Shore et al. 2019, Williams et al. 2020)

Chemo–hormonal therapy with docetaxel in addition to ADT was the first combination that was integrated in the clinical guidelines for patients with mHSPC (EAU 2020, National Comprehensive Cancer Network 2020). Not all patients with mHSPC may receive or are willing to undergo treatment with chemotherapy. As the clinical practice continues to evolve with new strategies and criteria to be considered for treatment decisions the overall treatment paradigm of mHSPC is currently under modification aiming to propose the most appropriate therapeutic options to different subgroups of patients with mHSPC including those who are not planned for chemotherapy. Darolutamide added to ADT has demonstrated a significant benefit and a favorable safety profile in nmCRPC and therefore, it is expected that darolutamide in addition to ADT will enhance disease control and will provide a significant benefit in patients with mHSPC compared to placebo plus ADT without compromising patient's quality of life.

Therefore, considering the unique safety profile of darolutamide, the present study will evaluate darolutamide in addition to ADT in mHSPC participants.

2.2 Background

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

Metastatic hormone-sensitive prostate cancer is the disease stage where patients have metastatic prostate cancer and are responsive to ADT including patients who develop metastatic recurrence after local treatment (surgery and / or radiotherapy) and patients with de novo metastatic disease who did not benefit from prior radical procedures.

Newly diagnosed mHSPC is recognized as an aggressive form of the disease with rapid progression to the metastatic castration-resistant state in virtually all patients (Fizazi et al. 2019, Vale et al. 2016). Historically, androgen deprivation, achieved by surgical or medical castration, has been the standard of care for mHSPC (Rydzewska et al. 2017). Although

almost all men with mHSPC initially experience a response to ADT, most will develop mCRPC within 1 to 3 years of their diagnosis (Fizazi et al. 2015, Gravis et al. 2013, Sweeney et al. 2015). Metastatic castration-resistant prostate cancer has poor prognosis and high lethality.

Metastatic hormone-sensitive prostate cancer has a well-documented course, and the treatment landscape has rapidly evolved over the last five years. Several randomized trials have demonstrated significant clinical benefit with the addition of docetaxel, abiraterone plus prednisone, enzalutamide or apalutamide to ADT (Cattrini et al. 2019, Hahn et al. 2018). However, the addition of those agents to ADT may induce acute and chronic morbidities. Strategies to avoid and/or diminish these morbidities should be considered, as the choice between ADT alone and ADT combined with docetaxel, abiraterone acetate, enzalutamide or apalutamide remains challenging (Cattrini et al. 2019, EAU 2020, Eliasson et al. 2017). Factors that are related to the tumor, patient condition, drug side effects or potential drug-drug interactions (DDI) together with patient preferences currently guide these clinical decisions (Cattrini et al. 2019). As an example, one discrete choice study that evaluated preferences of men with mCRPC and mHSPC in France, Germany and the UK found that they expressed a strong preference for treatment(s) that delays the initiation of chemotherapy (odds ratio [OR]: 1.727; 95% CI: 1.548-1.927) (National Comprehensive Cancer Network 2020).

Chemo–hormonal therapy with docetaxel in addition to ADT was the first combination that was integrated in the clinical guidelines for patients with mHSPC (James et al. 2016, Sweeney et al. 2015). As the clinical practice continues to evolve with new strategies and criteria to be considered for treatment decisions the overall treatment paradigm of mHSPC is currently under modification aiming to propose the most appropriate therapeutic options to different subgroups of patients with mHSPC.

2.3 Benefit/Risk Assessment

Darolutamide has undergone an extensive clinical development program and the data have demonstrated efficacy and effectiveness in the treatment of patients with mCRPC and nmCRPC.

Darolutamide's efficacy and tolerability have been demonstrated in two Phase 3 studies, 17712 (ARAMIS) and 17777 (ARASENS) (Smith et al. 2022).

In the randomized, double-blind placebo-controlled Phase 3 study 17712 (ARAMIS), including 1509 patients, darolutamide demonstrated an improvement in metastasis-free survival (MFS) and overall survival (OS) compared to placebo for nmCRPC patients with a rapid PSA doubling time (MFS: active arm median 40.4 vs 18.4 months in placebo arm, HR 0.41; 95% CI 0.34–0.50; P<0.0001; OS: at the time of primary analysis, darolutamide showed statistically significant OS benefit corresponding to a 31% reduction in the risk of death compared with placebo). Darolutamide showed a favorable safety profile, with similar incidence of most common treatment-emergent adverse events (TEAEs) and similar incidence of permanent discontinuations of treatment between the darolutamide and the placebo arms. No evidence was found that darolutamide would add any clinically relevant toxicity when administered with ADT. Importantly, patient quality of life was maintained throughout the duration of treatment. Based on the results of ARAMIS study, darolutamide was approved for the treatment of patients with nmCRPC.

In the randomized, double-blind, Phase 3 study 17777 (ARASENS), including 1306 patients, darolutamide, in combination with docetaxel and ADT treatment, showed survival benefit,

compared to placebo in combination with docetaxel and ADT, in mHSPC patients. The risk of death was significantly lower, by 32.5%, in the darolutamide group than in the placebo group (hazard ratio 0.68; 95% confidence interval, 0.57 to 0.80; P<0.001). Also, secondary endpoints favored darolutamide treatment arm. Adverse events were similar in the two groups, and the incidences of the most common adverse events (occurring in ≥10% of the patients) were highest during the overlapping docetaxel treatment period in both groups. The most commonly reported AEs were known toxic effects related to the docetaxel therapy. As AE of interest for the antiandrogen therapeutic class, in 17777 (ARASENS) trial only rash and hypertension showed a difference of incidence between the 2 arms which was >2 percent (rash was reported in 16.6% of the patients in the darolutamide group and 13.5% of those in the placebo group; hypertension was reported in 13.7% and 9.2%, respectively).

In the pooled analysis of safety in mCRPC patients from Phase 1/2 studies, the overall incidences of individual TEAEs were higher than seen in nmCRPC patients. This was expected considering that the mCRPC patients have more advanced disease with comorbidities. Despite the differences in the patient populations, the overall TEAE profile in the mCRPC pool was consistent with that observed in ARAMIS study supporting the favorable safety profile of darolutamide.

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

2.3.1 Risk Assessment

The safety profile of darolutamide therapy is well characterized based on the data from the ARAMIS and ARASENS studies in nmCRPC and mHSPC patients, respectively, as well as on integrated data from Phase 1 and 2 studies including patients with mCRPC. safety issues. Overall, the data show that darolutamide is well tolerated and has a favorable safety profile.

The overall safety profile of darolutamide is based on data from 1508 patients of whom 954 received at least one dose of darolutamide in the ARAMIS study, plus 1306 patients of whom 651 took at least one dose of darolutamide in the ARASENS study.

In ARAMIS, the good tolerability of darolutamide treatment was demonstrated by similar incidences of TEAEs leading to permanent treatment discontinuation between the treatment arms (8.9% darolutamide vs. 8.7% placebo) during the double-blind phase. The incidence of adverse events was low and generally similar in the darolutamide and placebo treatment arms; with the exception of fatigue, which was the only event reported in >10% of patients (13.2% darolutamide vs. 8.3% placebo). Rash, pain in extremity and fatigue adverse drug reactions were identified as adverse drug reactions; neutrophil count decreased, bilirubin and aspartate aminotransferase (AST) increased as laboratory test abnormalities for darolutamide.

The laboratory abnormalities were predominantly of grade 1 or 2 in intensity and not associated with any clinically relevant signs and symptoms and were either transient or reversible after treatment discontinuation. There was no incremental risk with the addition of darolutamide to ADT for events such as fall, seizure, hypertension. No evidence was found that darolutamide would add any clinically relevant toxicity when administered with ADT.

In ARASENS, incidence of TEAEs were similar in both treatment arms. The incidences of the commonly reported TEAEs (occurring in ≥10% of the participants), were highest in both treatment groups during the period when the participants received both docetaxel and either

darolutamide or placebo, and progressively decreased thereafter. The most commonly reported TEAE with grade 3 and grade 4 as worst grade, were white blood cell count decreased and neutrophil count decreased, respectively. Hypertension and rash were identified as adverse drug reactions, blood bilirubin increase, alanine aminotransferase (ALT) and AST increased as lab test abnormalities.

More detailed information about the known and expected risks and expected adverse events can be found in the Investigator's Brochure of darolutamide and Patient Information Leaflet, Package Insert of ADTs.

Cases of idiosyncratic hepatic reactions with increases in ALT and AST to ≥5 and ≥20 x upper limit of normal (ULN) have been reported in darolutamide clinical trials. Time to onset ranged from 1 month to 10.5 months after initiation of darolutamide. The ALT and AST elevations were reversible upon darolutamide discontinuation. Please see Sections 6.6.3 and 7.1.

2.3.2 Benefit Assessment

Darolutamide is a potent ARi with low blood–brain barrier penetration and low potential for drug–drug interactions. The present study will evaluate darolutamide in addition to ADT in mHSPC participants.

Darolutamide has a favorable safety profile based on the data from two the Phase 3 randomized, double-blind studies, i.e., ARAMIS study in nmCRPC and ARASENS in mHSPC patients, supported by the integrated safety data from studies in mCRPC patients.

In ARAMIS, most of the adverse events were generally mild and manageable. In ARASENS, incidence of the adverse events occurred in the period of concomitant treatment with chemotherapy.

In addition, in the ARAMIS study, darolutamide effect on cardiac repolarization was studied in a subset of 500 participants. There was no clinically significant effect on cardiac repolarization (QTc) detected. Treatment with darolutamide will allow greater flexibility for concomitant use with medication typically used in the elderly patient population. This overall good tolerability was further demonstrated by the fact that in mCRPC patients (ARAMIS) no increase in permanent treatment discontinuations due to TEAEs has been observed in the darolutamide arm as compared to the placebo arm.

In ARASENS, where patients received up to 6 cycles of chemotherapy, the combination of darolutamide and docetaxel did not result in more toxic effects than the combination of androgen-deprivation therapy and docetaxel alone.

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

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, and regular evaluation of risk benefit by an independent DMC, the potential risks identified in association with darolutamide in addition to ADT are justified by the anticipated benefits that may be afforded to participants with mHSPC.

Based on ARAMIS study, darolutamide provided a significant improvement in MFS and OS, as well as a significant benefit in extending time to pain progression, time to cytotoxic chemotherapy and time to first symptomatic skeletal event (SSE) in patients with nmCRPC. Patients treated with darolutamide maintained their quality of life.

Based on ARASENS data, darolutamide provided a significant improvement in OS and other clinically relevant endpoints such as time to development of CRPC, time to pain progression, time to the first SSE, time to initiation of subsequent anticancer therapy in the mHSPC setting, when given in association with docetaxel.

The benefits of darolutamide treatment outweigh the risks arising from its use. The risks are well understood and are appropriately managed with product labeling and routine pharmacovigilance. Taking into account the seriousness of the disease as well as the medical need for additional therapy in this population, the overall benefit-risk balance of darolutamide is considered favorable.

Darolutamide offers an effective treatment option without the addition of clinically relevant toxicity when administered with ADT. The compelling safety and DDI profile of darolutamide will positively impact clinical practice by improving the management of prostate cancer treatment in an elderly population with co-morbidities where polypharmacy is the norm.

3. Objectives and Endpoints

The purpose of this study is to evaluate the efficacy and safety of darolutamide in addition to ADT versus placebo plus ADT in participants with mHSPC. All the objectives listed in Table 3–1 will be analyzed at the primary completion. Only limited analyses will be conducted in the final analysis, i.e. OS and safety.

Table 3–1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS in participants with mHSPC	• rPFS assessed by central review based on RECIST v. 1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases
Secondary	
• To evaluate efficacy of darolutamide in addition to ADT compared to placebo plus ADT by improving OS, time to progress to CRPC, time to initiation of subsequent anti-cancer therapy, time to PSA progression, and undetectable PSA rates	• OS – key secondary endpoint • Time to CRPC • Time to initiation of subsequent anti-cancer therapy • Time to PSA progression • PSA undetectable rates (<0.2 ng/mL)
• To estimate the participant's quality of life benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving symptomatic time to pain progression	• Time to pain progression (BPI-SF)
• To assess the safety of darolutamide in addition to ADT compared to placebo plus ADT in participants with mHSPC	• AE assessments using NCI CTCAE (v.5.0)
Other pre-specified	
• To further evaluate efficacy of darolutamide in addition to ADT compared to placebo plus ADT by progression-free survival 2 as assessed by the investigator (PFS2)	• Progression-free survival 2 (PFS2) as assessed by the investigator, is defined as time from randomization to clinical, biochemical, or radiological disease progression under first subsequent anti-cancer therapy or death, whichever occurs first
• To estimate the participant's quality of life benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving time to first SSE	• Time to symptomatic skeletal event, defined as time from date of randomization to the date of first SSE
• To investigate tumor* and circulating biomarkers with the aim of elucidating the molecular profile of the participants potentially related to response to darolutamide • To assess changes in tumor molecular status in circulating tumor DNA obtained before, during treatment and after progression on darolutamide, with the aim of elucidating the molecular profile, modifiers of response and acquired resistance to darolutamide	• Alterations of markers related to prostate cancer and androgen receptor inhibition such as androgen receptor (AR) alterations, alternative AR splice variants (e.g. AR V7), PTEN loss
• To further investigate the study drug and similar drugs (e.g. mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to cancer and associated health problems*	• Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)*
• To estimate the participant's quality of life benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving time to deterioration in FACT-P total score • To estimate the benefit of darolutamide in addition to ADT compared to placebo plus ADT by improving time to first prostate cancer- related invasive procedures	• Time to deterioration in FACT-P total score **During the double-blind period: Time to first prostate cancer-related invasive procedures** • Time to first prostate cancer-related invasive procedure is defined as time from randomization to date of first prostate cancer-related invasive procedure

Abbreviations: ADT = Androgen Deprivation Therapy; AE = Adverse event; AR = Androgen receptor; ARi = Androgen receptor inhibitor; BPI-SF = Brief Pain Inventory-Short Form; CRPC = Castration-resistant prostate cancer; CT = Computed tomography; EBRT = External beam radiation therapy; FACT-P = Functional Assessment of Cancer Therapy-Prostate; mHSPC = Metastatic hormone-sensitive prostate cancer; MRI = Magnetic resonance imaging; NCI CTCAE = National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0); OS = Overall survival; PCWG3 = Prostate Cancer Working Group 3; PSA = Prostate-specific antigen; PTEN = Phosphatase and tensin homolog; QoL = Quality of life; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = Radiological progression-free survival; PFS2 as assessed by the investigator = Time from randomization to radiological disease progression under first subsequent anti-cancer therapy or death, whichever occurs first; SSE = Symptomatic skeletal event; TEAE = Treatment-emergent adverse event
* Not applicable for China.

4. Study Design

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled Phase 3 study to determine if darolutamide in addition to ADT is superior to placebo plus ADT by improving rPFS in participants with mHSPC. The study schema and SoA are provided in Section 1.1 and Section 1.3, respectively.

Approximately 665 participants who meet the eligibility criteria including confirmation of metastatic disease by central review (see Section 5.1 and Section 5.2) will be randomized in a 2:1 ratio to receive one of the following **study drugs**:

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

Participants will be stratified at randomization as follows:

- Presence of visceral metastases versus absence of visceral metastases assessed by central review
- Prior local therapy versus no prior local therapy

Background treatment: All participants must receive ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, started not earlier than 12 weeks before randomization, on a continuous basis.

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

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

Once results of the primary analysis are available, if they support a positive benefit/risk assessment for darolutamide considering feedback from the study Steering Committee and/or health authorities, an open-label phase may start. Following the unblinding, those participants who are on study treatment (darolutamide or placebo) will be offered the opportunity to receive darolutamide through open-label period in this study, at the discretion of the investigator. Those participants who do not choose to continue with open-label darolutamide treatment, will have an end-of-study treatment visit at the time of unblinding.

At the moment of unblinding, if participant qualifies to continue the study treatment, participant will be offered to enter the open-label phase. Open-label phase ICF must be signed before any study-related intervention. Participants in the open-label phase will continue to be assessed according to the SoA in Section 1.3.

To transition from the double-blind to open-label phase, participants who are on placebo arm will undergo an unscheduled visit to confirm they qualify to continue the study treatment, sign ICF and dispense open-label active drug. Participants who are on active arm will undergo subsequent scheduled regular study visit to, sign ICF and dispense open-label drug.

In the open-label phase, tumor assessments, including radiology assessments, PSA and testosterone will continue according to local practice and evaluated by local radiologists/laboratories. Scans will no longer be collected for the central radiology review. Upon discontinuation of the study drug, participant will continue the study in the active and subsequently Long-term Follow-up phase for collection of data relevant for selected endpoints (i.e., OS and safety).

4.1.1 Screening Period

The start of the screening period is defined by signing of the informed consent form (ICF).

Participant screening must occur within 28 days prior to randomization, during which all study-related procedures and evaluations will be performed in order to establish participant eligibility. Baseline computed tomography (CT)/magnetic resonance imaging (MRI) scans and bone scans should be submitted for central review as soon as possible during the screening period in order to complete confirmation of metastatic disease for eligibility and assess stratification for presence/absence of visceral metastases during the screening period. Screening procedures can be performed on separate occasions within the allowed 28-day timeframe. It is estimated that it will take 7 to 14 days to obtain results from the safety laboratory assessments, testosterone, and PSA.

Each participant’s eligibility will be double-checked by the Bayer–designated medical representative (contract research organization [CRO] Medical Monitor) in writing. The investigator will complete a paper eligibility form confirming the key inclusion and exclusion criteria. This form will be forwarded to the Bayer–designated medical representative for review and eligibility double-check, which will take into account the results of the central image review for eligibility. Central review imaging will also provide stratification (visceral disease present vs. visceral disease absent). The responsibility of a participant’s enrollment remains with the investigator.

Timing for sending the scans to the imaging core laboratory, central review of images, sending the eligibility form and its review will have to be taken into account when planning the screening procedures.

Screening will take place in the Interactive Web Response System (IWRS), where the participant will receive a unique identification (ID).

At the end of the screening period, eligible participants (eligibility documented and confirmed) will be randomized to receive study drug as described in Section 4.1.

The screening period only applies to the double-blind phase of the study.

4.1.2 Treatment Period

The start of the treatment period is defined by the first administration of study drug, which has to occur within 3 days since randomization and after all activities described in the SoA (Section 1.3) Visit 1, Day 1 have been conducted.

During treatment period, participants will be evaluated with regular clinic visits every 12 weeks (±7 days) for efficacy and safety as described in the SoA (Section 1.3). Date of visit is to be calculated based on the previous visit date.

The dose or dosing schedule of the study drugs may be modified following the occurrence of adverse events (AEs) according to the guidance provided in Section 6.6.

The treatment period can take place either in the double-blind or both in the double-blind and open-label phases.

In the double-blind period, participants will receive study drug until documented radiological disease progression assessed by central review, unacceptable toxicity or until any other withdrawal criteria specified in Section 7.1 is met. In the open-label phase same discontinuation criteria apply, but radiological tumor assessments will continue according to local practice and will be evaluated by local radiologists.

An independent Data Monitoring Committee (DMC) will monitor the unblinded safety data on a regular basis throughout the trial, until primary completion. Participants will have a safety follow-up visit 30 days (+7 days) after last dose of study drug or prior to initiating of new anti-cancer therapy for prostate cancer whichever occurs first.

After final OS analysis of the current study participants ongoing on darolutamide treatment may continue to receive darolutamide in the current study or in a separate access program (roll-over study or any other mechanism to supply drug post-study). This is subject to approval by the competent health authority and ethics committee.

The treatment period will end at each site when all participants at the site who are ongoing on darolutamide treatment have transitioned into a separate access program (roll-over study or any other mechanism to supply drug post-study) to continue receiving darolutamide (see Section 6.7) or have discontinued from the study treatment.

4.1.3 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.

In both the double-blind and open-label phases of the study, **End of Treatment (EOT) visit** will be conducted 30 days (+7 days) after the last dose of study drug.

For the participants who, at the start of open-label period, do not qualify or refuse to enter the open-label phase of the study, EOT will be performed.

Another systemic anti-cancer therapy may be initiated no sooner than 7 days after the last dose of study drug. For participants for whom another systemic anti-cancer therapy is planned to start sooner than 30 days (+7 days) after the last dose of the study drug, the EOT visit must be conducted before the new anti-cancer therapy starts.

During the EOT visit, procedures to monitor participant’s health, to identify potential toxicities, and to assess efficacy will be performed as described in the SoA tables (Section 1.3).

Active Follow–up visits will start after completion of the EOT evaluation: approximately 5 Active Follow–up visits will occur as standard of care clinic visits approximately every 12 weeks, for approximately 1 year (12 ±1 months).

In the double-blind phase, Active Follow-up visits are meant to record survival status, SSEs, efficacy (CT/MRI and bone scan), PSA and testosterone for participants who discontinue the study treatment before radiological progression assessed by central review, prostate cancer-related invasive procedure until change of anti-cancer therapy, QoL, pain assessment, subsequent anti-cancer treatments for prostate cancer, and study drug-related SAEs with concomitant medication received.

Instructions for imaging in the Active Follow-up phase in the double-blind phase of the study, for participants who discontinued study drug before radiological progression assessed by central radiology review:

- Contrast enhanced CT/MRI and bone scan will be performed every 12 weeks until radiological disease progression is assessed by central review.
- If allowed by local regulations, participants without centrally-assessed radiological disease progression, for whom start of a subsequent anti-cancer therapy is planned before the next follow-up visit/contact, should perform a tumor assessment (contrast enhanced CT/MRI and bone scan) and submit it to the core imaging laboratory for central radiology review. Note that this tumor assessment is not required if the prior tumor assessment was performed within the previous 30 days.

Participants for whom radiological disease progression was already assessed by central review, will continue imaging as per local practice.

In the open-label phase of the study, Active Follow-up visits are meant to record survival status and study drug-related SAEs with concomitant medication received.

Date of clinical, biochemical, or radiological disease progression under first subsequent anticancer therapy, as assessed by the investigator, will be reported in the electronic case report form (eCRF).

The Active Follow–up period extends from the discontinuation of treatment period for approximately 1 year (12 ±1 months) or until the participant 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.

4.1.4 Long–term (survival) Follow–up Period

In both double-blind and open-label study phases, after completing the Active Follow–up period, participants will enter the Long–term Follow-up period and will be contacted approximately every 12 weeks (by telephone) to record survival status, subsequent anti-cancer treatments for prostate cancer and prostate cancer-related invasive procedure until change of anti-cancer therapy, (only applicable to the double-blind phase), and study drug-related SAEs with concomitant medications received until death, lost to follow-up, consent withdrawal, or the sponsor terminates the study.

Limited to the double-blind phase of the study, in case that a participant did not experience radiological disease progression assessed by central review or did not start a subsequent anti-cancer treatment within the end Active Follow-up, radiological assessments by CT/MRI and bone scan must continue in the Long-term Follow-up. If allowed by local regulations, participants without centrally-assessed radiological disease progression, for whom start of a

subsequent anti-cancer therapy is planned before the next follow-up visit/contact, should perform a tumor assessment (contrast enhanced CT/MRI and bone scan) and submit it to the core imaging laboratory for central radiology review. Note that this tumor assessment is not required if the prior tumor assessment was performed within the previous 30 days.

Also, PSA and testosterone central assessments should continue in long term follow-up for participants not experiencing radiological disease progression by central review, until it occurs, or a new anti-cancer treatment is started. Therefore, in that case participants should continue with clinic visits during long term follow-up.

The information will be collected as described in the SoA (Section 1.3).

Pertaining to the information that will be collected over the telephone from the participant, it is the clinical site's responsibility to obtain and make available the source documentation for the information collected from the participant and documented it in the source data and recorded in the eCRF.

Survival Sweep
For the primary analysis and subsequent overall survival (OS) analyses, the survival data will be collected through additional survival sweeps. All participants considered alive shortly after the database cut-off date for the primary analysis and prior to any subsequent analysis of OS will be contacted for survival status.

4.2 Scientific Rationale for Study Design

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

Despite the recent combinations approved for patients with mHSPC, the ADT alone still to be standard of care in many countries. The ADT alone as comparator arm is consistent with other pivotal study designs conducted in mHSPC, and therefore important to study in this patient populations who are often on these medications for a significant period.

Darolutamide, added to ADT has demonstrated a significant benefit and a favorable safety profile in nmCRPC and therefore, it is expected that darolutamide in addition to ADT will enhance the disease control and will provide a significant benefit in patients with mHSPC compared to ADT while preserving patient's quality of life without increasing the incidence of adverse events.

The primary endpoint of this study will be radiological progression-free survival (rPFS) utilizing conventional imaging methods ^{99m}Tc-bone scan for bone metastases according to Prostate Cancer Working Group 3 (PCWG3) (Scher et al. 2016) [Appendix 10, Section 10.10] criteria and CT/MRI for soft tissue/visceral metastases based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v. 1.1) (Eisenhauer et al. 2009) [Appendix 9, Section 10.9] criteria. In the recently reported pivotal trials in mHSPC, rPFS has been used as the sole primary endpoint or as part of a dual endpoint (Armstrong et al. 2019, Fizazi et al. 2017).

Metastatic hormone-sensitive prostate cancer is a complex disease and trials that make use of OS as a primary outcome in mHSPC can take close to a decade to complete and are subject to issues with crossover. Therefore, rPFS as the primary endpoint may be used as a surrogate endpoint to OS that is available earlier and that can be measured more frequently than OS. For patients with localized prostate cancer it has been shown that MFS is a strong surrogate for

OS based on an analysis of 20 trials and 13,000 men with localized prostate cancer conducted by the Intermediate Clinical Endpoints in Cancer of the Prostate program (ICECaP M0) and is currently accepted for nmCRPC (Xie et al. 2017).

Based on the positive outcome of ICECaP M0, the STOPCAP M1 program aims to identify whether other endpoints could be potential surrogate endpoints for OS in mHSPC (Tierney et al. 2019). Besides, recently enzalutamide was approved in addition to ADT for patients mHSPC based on rPFS improvement reported in ARCHES trial (Armstrong et al. 2019).

Overall, this study will evaluate approximately 665 participants randomized 2:1. Overall survival will be the key secondary endpoint and the interim analysis of OS will occur at the time of the rPFS analysis. The stopping boundaries for the two OS analyses will be calculated with an O'Brien-Fleming alpha-spending function based on the actual number of events observed up to the cut-off dates.

Once results of the primary analysis are available, if they support a positive benefit/risk assessment for darolutamide considering feedback from the study Steering Committee and/or health authorities, an open-label phase may start.

4.2.1 Participant Input into Design

For this study participant input into design was not assessed.

4.3 Justification for Dose

The recommended oral dose was determined based on non-clinical results and clinical results from studies 17829 (ARADES), 17830 (ARAFOR) and 17712 (ARAMIS).

Clinically, darolutamide has been studied in dose range from 100 mg to 900 mg bid in the dose-escalation and dose finding study 17829 (ARADES). Dose-linearity of the pharmacokinetic parameters was observed after single and repeated administration in the dose range of 100 mg and 700 mg darolutamide bid. At higher dose (900 mg bid), no further increase in exposure or maximum concentration of darolutamide was observed, indicating that saturation of absorption occurs at doses higher than 700 mg of darolutamide bid.

Study 17830 (ARAFOR) was conducted using a dose of 600 mg darolutamide bid, a dose selected based on non-clinical efficacy data in mice showing maximum PSA suppression at an exposure level of unbound darolutamide to be expected at a dose of 600 mg darolutamide bid. Based on biopharmaceutical characteristics, antitumor activity and safety profile, the dose of 600 mg bid was selected for subsequent clinical studies.

In a randomized, double-blinded, placebo-controlled Phase 3 study 17712 (ARAMIS), this recommended dose of 600 mg darolutamide bid demonstrated statistically significant clinical benefits in nmCRPC patients as mentioned above (see Section 2.3).

4.4 End of Study Definition

The study starts with a double-blind phase. **Primary completion** will be reached when the planned number of events for the primary endpoint is reached (see Section 9.4.2.1). Once results of the primary analysis are available, if they support a positive benefit/risk assessment for darolutamide considering feedback from the study Steering Committee and/or health authorities, an open-label phase may start.

The **end of the study** as a whole will be reached as soon as the last visit of the last participant has been reached in all centers in all participating countries.

A participant is considered to have completed the study if he has undergone all periods of the study described in Section 4.1, and has transitioned into a separate access program (roll-over study or any other program to supply drug post-study, where possible) or has discontinued the study for another reason (e.g., death, lost to follow–up, consent withdrawal with no further data collection).

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

At each site, when all participants on darolutamide treatment have transitioned into the separate access program or have discontinued the study for another reason (e.g. lost to follow–up, consent withdrawal), those participants who are in follow-up will discontinue as the current study will be terminated.

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

5. Study Population

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

The study population includes participants with a diagnosis of mHSPC.

5.1 Inclusion Criteria

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

1. Written informed consent obtained.
   Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Males ≥18 years of age.
3. Histologically or cytologically confirmed adenocarcinoma of prostate.
4. Documented metastatic disease by conventional imaging method either by a positive ^{99m}Tc-phosphonate bone scan, or soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by central review. Note: participants with a baseline "superscan" (bone scan showing a diffuse, intense, skeletal uptake of the tracer with absent renal and background activity) are considered ineligible.

   Note: 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 RECIST version 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.

   Regional lymph node metastases **only** (N1, below the aortic bifurcation) will not be considered as metastases eligible for the study. Only participants with non-regional lymph node metastases (M1a) and/or bone metastases (M1b) and/or other sites of metastases with or without bone disease (M1c), assessed according to National Comprehensive

Cancer Network (NCCN) classification, will be eligible. (National Comprehensive Cancer Network 2020)

5. Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first generation anti–androgen, but not earlier than 12 weeks before randomization. For participants receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 14 days prior to randomization is recommended.
6. First generation anti–androgen must be discontinued at least 1 day before study treatment start.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1 or 2.
8. Blood counts at Screening: hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥1.5x10^9/L, platelet count ≥100x10^9/L (participant 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 aspartate aminotransferase (AST) ≤1.5 x ULN, total bilirubin ≤1.5 x ULN, creatinine ≤2.0 x ULN (for Canada: Screening values of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 x ULN, total bilirubin ≤1.5 x ULN).
10. Sexually active male participants must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the treatment with study drug and for 4 weeks after the last dose of the study treatment with study drug.
11. For Canada: At Screening; estimated glomerular filtration rate (eGFR) eGFR ≥30 mL/min/1.73 m^2 (calculated by the CKD-EPI formula, (Levey et al. 2009).

5.2 Exclusion Criteria

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

1. Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate.
2. Known brain/ leptomeningeal metastases
   Note: Brain CT/MRI scan should be performed only in case of symptoms.
3. Prior treatment with:
   - LHRH agonist/antagonists started >12 weeks before randomization starts except neoadjuvant and /or adjuvant therapy for a duration ≤24 months and completed ≥12 months prior to randomization
   - Second–generation androgen receptor (AR) inhibitors such as enzalutamide, darolutamide, apalutamide or other investigational AR inhibitors
   - Cytochrome P 17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as anti-cancer treatment for prostate cancer
   - Chemotherapy including docetaxel or immunotherapy for prostate cancer
   - Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days prior to randomization

- Radiopharmaceuticals
- Any other anti-cancer treatment for prostate cancer, excluding local therapies and ADT

4. Treatment with radiotherapy (external beam radiation therapy [EBRT], brachytherapy) within 2 weeks before randomization.
5. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation of the study drugs.
6. Contraindication to iodinated CT and gadolinium chelate MRI intravenous contrast agent(s).
7. Any prior malignancy (other than adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) within 5 years prior to randomization.
8. An active viral hepatitis (defined as Hepatitis B surface antigen [HBsAg] reactive or detectable [qualitative] hepatitis B virus [HBV] DNA or defined as hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] is detected), known human immunodeficiency virus (HIV) infection with detectable viral load, or chronic liver disease with a need of treatment.
   Note: No testing for Hepatitis B and/or Hepatitis C is required unless mandated by local authority. No HIV testing is required unless mandated by local authority.
9. 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).
10. Uncontrolled hypertension as indicated by a resting systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 100 mmHg despite medical management.
11. A gastrointestinal (GI) disorder or procedure which is expected to interfere significantly with absorption of study drug.
12. 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).
13. Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the participant and/or his/her compliance with study procedures or may interfere with the participant's participation in the study or evaluation of the study results.
14. Inability to swallow oral medications.

5.3 Lifestyle Considerations

There are no lifestyle considerations for participant's eligibility for the study.

5.3.1 Meals and Dietary Restrictions

There are no meals and dietary restrictions for participants participating in this study.

5.3.2 Activity

There are no specific activity restrictions for participants participating in this study.

5.4 Screen Failures

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

A participant who, for any reason (e.g., failure to fulfill the eligibility criteria), terminates the study at any time prior to randomization is regarded a “screen failure”. The reason will be documented in the source documentation and the eCRF and the participant will discontinue participation in study with no further follow–up required. Screen failure must be completed in the IWRS.

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, participant should be considered a screen failure.

Participants who do not meet the criteria for participation in this study (screen failure) may be re-screened within 2 weeks from the prior screen failure date.

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

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

Re–screening of a participant who did not fulfill the eligibility criteria is allowed within 2 weeks from the prior screen failure date. If the participant meets criteria for re-screening, then this step must be completed in the IWRS, and the participant will be assigned a new ID.

Re–screening of screen failed participants may only be allowed once after discussion with the Bayer–designated medical representative. Sponsor approval may be required on case by case evaluation. Approval of re–screening for a screen failed participant must be documented.

6. Study Intervention

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

6.1 Study Interventions Administered

Study drugs

The following study drugs are administered in this study:

- Darolutamide (BAY 1841788) or
- Placebo matching darolutamide

The term "study drug" used in this protocol refers to either of these drugs. If either only darolutamide or placebo is described, the respective drug name will be used. Details on study drugs are provided in Table 6–1.

Background treatment

In both double-blind and open-label periods, all participants must receive ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, not earlier than 12 weeks before randomization, on a continuous basis.

For participants receiving LHRH agonists, treatment in combination with a first generation anti–androgen for at least 14 days prior to randomization is recommended. First generation anti–androgen will be discontinued 1 day before study treatment start.

The concurrent treatment with a LHRH agonist/ antagonists will be provided by the local/ site pharmacy and the dose and schedule of administration will be consistent with the local prescribing information approved.

The concurrent therapy with LHRH agonist/ antagonists or orchiectomy must be documented in the source data and recorded in the eCRF.

Table 6–1 Administration of study drug

Study Drug Name	Darolutamide	Placebo
Type	Drug	Drug
Dose Formulation	Coated tablet	Coated tablet
Unit Dose Strength(s)	300 mg / tablet	Not applicable
Dosage Levels	600 mg twice daily	Twice daily
Route of Administration	Oral	Oral
Additional administrative information		
Use	Active test drug	Inactive comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study drug will be provided in 150ml HDPE bottles with child resistant closure, each containing 140 tablets. Each bottle will be labeled as required per country requirement.	Study drug will be provided in 150ml HDPE bottles with child resistant closure, each containing 140 tablets. Each bottle will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Darolutamide (INN), BAY 1841788	Placebo to darolutamide

Abbreviations: HDPE = High density polyethylene, IMP = Investigational medicinal product; INN = International nonproprietary name; NIMP = Non-investigational medicinal product.

Participants will be instructed to take 2 tablets of study drug orally twice daily at approximately 12 hour intervals as close to the same time each day as possible.

The tablets should be taken with food and a glass (about 250 ml) of water. The tablets should be swallowed whole.

The first dose of study drug will be administered with breakfast at the study center. Participants will continue taking study drug at home throughout the study treatment period and will be instructed to take their morning dose of study drug at home on further visit days.

Participants will receive study drug until any withdrawal criteria specified in Section 7.1 is met.

Dose modifications (interruption or reduction) due to study drug-related AEs are described in Section 6.6. For reduced dose, participants will be instructed to take 1 tablet of study drug orally twice daily with food at approximately 12 hour intervals as close to the same time every day as possible. If dosing is missed, it can be taken up to 6 hours from the planned dosing time to make up for the missed one.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drugs.
2. Only participants enrolled in the study may receive study drugs and only authorized site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in

accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Study drug returns, reconciliation, and destruction may be captured in study drug reconciliation and destruction logs.
4. Further guidance and information for the final disposition of unused study drugs are provided in the Study Reference Manual or other specified location.

6.3 Measures to Minimize Bias: Randomization and Blinding

Table 6–2 Randomization and Blinding by using Interactive Web Response System (IWRS)

Study using IWRS	All participants will be centrally assigned to randomized study drug using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each site. Study drug will be dispensed at the study visits summarized in SoA (Section 1.3). Returned study drugs should not be re-dispensed to the participants. Potential bias will be reduced by central randomization.
Blind Break (IWRS)	The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Abbreviations: IWRS = Interactive Web Response System; SoA = Schedule of Activities

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

Treatment assignments of participants randomized to study drug will be done centrally using IWRS. A computer-generated randomization list will be generated by the sponsor or delegate for random assignments and provided to the IWRS vendor. The randomization number will be assigned to the participant through the IWRS 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 will be packaged in bottles labelled with a unique kit number. The study kit number will be assigned to the participant through the IWRS.

Participants will be stratified as follows:

- Presence of visceral metastases versus absence of visceral metastases assessed by central review
- Prior local therapy versus no prior local therapy

The DMC will regularly review in an unblinded manner the safety data of participants who were randomized and have received at least 1 dose of study drug. The investigators, the participants and the sponsor will remain blinded.

6.3.1 SUSAR Unblinding

In the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see Section 10.3) related to the blinded treatment, the participant'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.

6.3.2 Unblinding by the Investigator

Investigators may only unblind participants under following unblinding rules.

If a participant is unblinded by the investigator, they must discontinue study drug.

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.

If emergency unblinding is necessary for the treatment of a participant for an SAE, the treatment with study drug can be unblinded via the IWRS system (refer to the IWRS manual for instructions). The participating site has unrestricted and immediate access to break the treatment code in IWRS. Should the blinded code be broken for a participant for emergency, the Medical Monitor or designee should be contacted by the principal investigator (PI) within 24 hours of unblinding to discuss the rationale.

Unblinding may also be performed after the participant discontinues study treatment because of radiological progression assessed by central review, and the investigator feels this information is essential to determine the next course of therapy. Unblinding a participant for this situation may only take place after discussion with the sponsor's medical monitor or designee.

6.4 Study Intervention Compliance

Participants will self-administer study drug (study intervention) at home, compliance with study drug will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc. Study site personnel will instruct participants to report the time when study drug is self-administered. Participant compliance with study drug will be assessed at each visit. Deviation(s) from the prescribed dosage regimen should be documented in the source data and recorded in the eCRF. Compliance will be assessed during the site visits and documented in the source documents.

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. An adequate record of receipt, distribution, and return/destruction of all study treatment must be captured on the dispensing log and drug accountability form.

Study drug tablets not returned will be considered to have been taken unless otherwise specified. At the end of the study, any remaining study drugs will be collected and returned to the sponsor, destruction depot, or destroyed at the site. Any discrepancies between the returned and expected returned study drugs should be explained.

6.5 Concomitant Therapy

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

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

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

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

All concomitant treatments from the time of informed consent (IC) until the end–of–study treatment visit must be recorded on the CRFs. Once the participant 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 anti-cancer therapy for prostate cancer.

Contrast media do not need to be recorded as concomitant medication unless there is an adverse event related to its administration (e.g., allergic reaction).

6.5.1 Permitted Concomitant Therapy

Analgesic use will be captured via eCRF. Investigators or designees are to record which opioid and non-opioid medications were used since the last visit, and investigators or designees 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) (Section 8.1).

Palliative radiation therapy or surgical intervention as needed are allowed during study treatment.

Vaccines for COVID-19, and flu are permitted during study treatment (see Section 6.5.2).

All participants must receive ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, on a continuous basis. Switching ADT to an LHRH agonist/antagonist is permitted during study treatment, the reason and the time of LHRH treatment modification must be documented in the source data and recorded in the eCRF.

Administration of 600 mg darolutamide bid over 4 days prior to administration of a single dose of 5 mg rosuvastatin, a breast cancer resistance protein (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 may also increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g., methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the participants 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.

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

Contrast agents for radiological assessments are not required to be recorded in the Concomitant Medication CRF page, unless there is an adverse event related to the administration of contrast (e.g., contrast media allergic reaction) or the procedure is experimental and/or using an experimental contrast material (e.g., contrast enhanced ultrasound to determine vascularity).

6.5.2 Prohibited Concomitant Therapy

Concomitant treatment with another systemic anti-cancer therapy or another investigational medicinal product is prohibited with the exception of ADT throughout the study 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 including docetaxel
- Enzalutamide, apalutamide, bicalutamide, flutamide, nilutamide
- Abiraterone acetate or other CYP17 inhibitors
- Systemic ketoconazole as anti-cancer treatment for prostate cancer
- Any other anti-cancer treatment for prostate cancer, excluding local therapies and ADT

Any new systemic anti-cancer therapy may be initiated no sooner than 7 days after the last dose of study drug.

Use of live, attenuated, replication-competent vaccines is not permitted.

Darolutamide is a substrate of CYP3A4 and P-glycoprotein (P-gp). Repeated administration of rifampicin (600 mg), a strong CYP3A4 and a P-gp inducer, with a single dose of darolutamide (600 mg) together with food, resulted in a decrease of 72% in mean exposure [AUC(0-72)] and a decrease of 52% in C_{max} of darolutamide. Use of strong CYP3A4 inducers

and P-gp inducers (e.g., carbamazepine, phenobarbital, St. John's Wort) during treatment with darolutamide is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.

6.6 Dose Modification

The dose or dosing schedule of the study drug may be modified following the occurrence of AEs. Doses of study drug may be interrupted or reduced in case of clinically significant toxicities that are considered by the investigator to be related to study drug.

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

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

If a participant experiences several study 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.

6.6.1 Dose Interruption

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

6.6.2 Dose Reduction

If considered necessary for participant's safety, the dose of study drug may be reduced to 300 mg bid.

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

6.6.3 General Requirements for Dose Modifications of Study Drug

A participant who experiences a Grade 3 or 4 study drug-related TEAE should interrupt study drug until the TEAE improves to Grade ≤2 or baseline status. Treatment with study drug is then to be restarted at 300 mg bid.

For Canada: For participants who experience a decreased renal function to severe renal impairment (eGFR of 15 to 29 mL/min/1.73 m^2, calculated by the CKD-EPI formula, (Levey et al. 2009), the dose adjustment to 300 mg twice daily of darolutamide is recommended.

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

Additional details are provided in Table 6–3.

Table 6–3 Study drug dose modifications

Severity grade (NCI–CTCAE v 5.0)	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	Interrupt until ≤ Grade 2 or baseline [a] When the severity is Grade ≤2 or baseline, restart at a reduced dose of 300 mg bid [b,c]	If Grade ≥3 study drug-related TEAE occurs while the participant is on a dose of 300 mg bid (following temporary or permanent dose reduction) the participant must be withdrawn from treatment with study drug

Excludes clinically nonsignificant and asymptomatic laboratory abnormalities.
Abbreviations: AE = Adverse event; bid = Twice daily; NCI–CTCAE v 5.0 = National Cancer Institute–Common Terminology Criteria for Adverse Events version 5.0; TEAE = Treatment-emergent adverse event
a: If there is no recovery after 28 consecutive days, treatment with study drug should be permanently discontinued.
b: When AE returns to baseline or is resolved, re-escalation to 600 mg bid may be considered by the investigator.
c: If, following a re-escalation to 600 mg bid a second Grade ≥3 study drug-related TEAE occurs, a permanent dose reduction to 300 mg bid is required. A third occurrence of a Grade ≥3 study drug-related TEAE requires permanent discontinuation of treatment with study drug.

6.7 Intervention after the End of the Study

If the study is stopped for any reasons but benefits are observed for participants, treatment options will be discussed and agreed between the investigators, the sponsor and the participants.

They may receive further treatment, assessments and/or be followed via a roll-over study or any other mechanism to supply drug post-study. This applies to participants on treatment and in follow-up.

In the event that a roll-over study or any other mechanism to supply drug post-study is established, the present study will end when all participants have transitioned or discontinued from this study for another reason (e.g. consent withdrawn, lost to follow-up, death, sponsor decision). Until the transition, participants will continue to follow all the procedures and visits required in the current version of the protocol.

However, the sponsor reserves the right to terminate access to study drug, in particular if any of the following occur:

a. the study is terminated due to safety concerns or lack of proven efficacy;
b. the marketing application is rejected by a health authority;
c. the participant can obtain medication used in this study as treatment from a government sponsored or private health program;
d. the clinical development of the drug is stopped, no marketing authorization is pursued, and therapeutic alternatives are available in the local market.

In case participants are transferred to a roll-over study or any other mechanism to supply drug post-study, drug formulation and / or dosage might change compared to the present study depending on the course of the clinical development.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1 Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study drug. If study drug is definitively discontinued, the participant will remain on the study for follow-up of primary, secondary, and other pre-specified endpoints. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study drug, in follow-up, and for any further evaluations that need to be completed.

Participants must be discontinued from the study treatment if any of the following occurs:

In the double-blind period:

- Radiological disease progression assessed by central review;

  Note: participants who experience a clinical benefit may continue the study treatment beyond radiological progression, according to PCWG3 guidelines, after agreement between the investigator and the sponsor or designee.
- If, in the investigator's opinion, continuation of the study drug would be harmful to the participant's wellbeing. If a participant experiences a clinical progression by worsening of disease signs/symptoms leading to study treatment discontinuation, radiological evaluations must be continued until radiological progression is assessed by central review or subsequent anti-cancer therapy is started.
- Start of new anti-cancer therapy
- Unacceptable toxicity
- Study drug interruption >28 consecutive days
- Darolutamide dosing below 300 mg bid
- Occurrence of Grade ≥3 study drug-related TEAE while the participant is on 300 mg bid
- Participants must be discontinued from the study treatment in case of hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug. (See Appendix 4, Section 10.4).

PSA increase or PSA progression should not trigger discontinuation of study treatment unless, radiological progression was assessed by central review.

In the open-label phase:

- Radiological disease progression assessed by local review or clinical progression assessed by the investigator.

  Note: participants who experience a clinical benefit may continue the study treatment beyond radiological progression, according to PCWG3 guidelines, after agreement between the investigator and the sponsor or designee.

- If, in the investigator's opinion, continuation of the study drug would be harmful to the participant's wellbeing.
- Start of new anti-cancer therapy
- Unacceptable toxicity
- Study drug interruption >28 consecutive days
- Darolutamide dosing below 300 mg bid
- Occurrence of Grade ≥3 study drug-related TEAE while the participant 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 participants who discontinue the treatment period for any reason. These participants are to be encouraged to remain on the study for follow-up of primary endpoint (i.e., until radiological progression is assessed by central review) and also secondary and other pre-specified endpoints (i.e., continue in the Active Follow–up period or Long–term Follow–up period). Participants are expected to participate in follow–up unless they explicitly object. Withdrawal of consent should be documented in the participant medical file.

7.1.1 Temporary Discontinuation

For a guidance on dose modifications, see Section 6.6.

7.1.2 Rechallenge

Participants who experienced TEAE requiring temporary discontinuation of study treatment may be rechallenged to the reduced dose (300 mg bid) or the full dose (600 mg bid) at discretion of the investigator. After a temporary dose reduction, rechallenge to the full dose (600 mg bid) can be considered if appropriate in investigator's opinion.

For further details regarding dose modifications for study drug-related TEAEs dose modifications and rechallenge, please see Section 6.6.3.

All dose modifications should be reported with start and stop dates in the eCRF.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants must withdraw 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 participant may decline to participate further. The participant will not suffer any disadvantage as a result.
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- Sponsor terminates the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, and additionally requests destruction of her/his samples taken but not yet tested, the investigator must document this (either destruction by site or request to central lab, as applicable) in the site study records.

7.3 Lost to Follow-up

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

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

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

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participant meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., CT/MRI/bone scan) performed within 42 days prior to start of treatment and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Randomization must occur within 28 days from ICF signature. The participant 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. Participants will continue taking study drug at home throughout the study treatment period and will be instructed to take their morning dose of study drug at home on further visit days.
- Control assessments (unscheduled visits) may be performed at any time during the study treatment period according to the judgment of the investigator.

8.1 Efficacy Assessments

Participants in the double-blind period will be evaluated every 12 weeks for:

- Disease progression by conventional imaging methods (CT/MRI and bone scan)
- Castration–resistant prostate cancer (CRPC), initiation of subsequent anti-cancer therapy, symptomatic skeletal events (SSEs), pain progression (BPI-SF questionnaire), first prostate cancer-related invasive procedure
- PSA assessment until confirmed radiological progression of the disease or change of anti-cancer therapy.
- Survival status
- In the open-label phase, the efficacy assessment will continue with recording of survival status. Tumor assessments, including radiology assessments, PSA and testosterone will continue according to local practice and evaluated by local radiologists/laboratories. Scans will no longer be collected for the central radiology review. Also, collection of data related to other prespecified endpoints will stop.

Refer to the SoA (Section 1.3) for detailed timing of efficacy assessments, and to Section 9.4.2 for definitions and analyses of efficacy endpoints. RECIST 1.1 will be utilized for tumor response assessment of metastatic soft tissue lesions (lymph nodes and visceral lesions) and metastatic bone lesions will be assessed according the PCWG3 criteria for bone lesions (Eisenhauer et al. 2009, Scher et al. 2016) (Appendix 9, Section 10.9 and Appendix 10, Section 10.10). This study will utilize both tumor assessments by the local investigator and by central review as described below.

Imaging during the double-blind phase of the study:

The preferred and recommended imaging modality for soft tissue tumor assessments is multi-detector CT with both oral and intravenous (i.v.) contrast. Anatomic coverage should be chest, abdomen and pelvis at all timepoints. MRI with i.v. gadolinium chelate-based contrast may be performed in lieu of contrast-enhanced CT when institutional policy does not recommend the use of CT or there is a contraindication to i.v. iodinated CT contrast. It is recommended that, when MRI is used, the abdomen and pelvis be performed with MRI. The chest should still be assessed with CT (with i.v. contrast if no contrast allergy, otherwise without contrast). If a participant develops a contraindication to CT contrast media during the course of the study after the baseline imaging, contrast enhanced MRI may be used in lieu of abdominal and pelvic CT and a non-contrast chest CT may performed in lieu of a contrast-enhanced chest CT. At screening, a participant suspected of having brain/ leptomeningeal metastases, should undergo brain CT or MRI with contrast to exclude such lesions.

The imaging modality for assessment of metastatic bone lesions is ^{99m}Tc-phophonate whole body bone planar scans acquired in anterior and posterior projections. The preferred radiotracer is ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) but other commercially available ^{99m}Tc-phosphonate radiotracers such as hydroxymethylene diphosphonate (HMDP) or hydroxyethylene diphosphonate (HDP) or 2,3-dicarboxypropane-1, 1-diphosphonate (DPD) may also be used in accord with local site practice.

For consistency, the same imaging modality and equivalent technique (e.g., slice thickness, field of view for CT/MRI; same ^{99m}Tc-phosphonate tracer for bone scans) should be used for all scans and tumor assessments across all time points performed on an individual participant,

including screening / baseline scans. Slice thickness for CT and MRI is strongly recommended to be ≤ 5mm.

The time points for chest, abdomen and pelvic CT/MRI scans and bone scans are described in the SoA (Section 1.3).

The baseline radiological tumor assessment will be conducted within 28 days before start of study treatment. Note that CT/MRI scans or bone scans performed as standard of care within 42 days prior to start of treatment are acceptable as screening scans provide that they meet the imaging requirements of this study (see Section 8.1 and the Imaging Guidelines that will be provided to the sites).

Subsequent CT/MRI and bone scans should then be performed every 12 weeks until radiological progression as assessed by central review or start of subsequent anti-cancer therapy. Participants who discontinued the study drug without radiological disease progression will continue the schedule of imaging assessment until radiological disease progression is assessed by central review or start of subsequent anti-cancer therapy. This will also happen in the Long-term Follow-up period for participants who did not have radiological progression assessed by central review or did not start subsequent anti-cancer therapy within the end of Active Follow-up. After radiological progression has been confirmed by central review or subsequent anti-cancer therapy has started, imaging will be performed according to local clinical practice. Date of clinical, biochemical, or radiological disease progression under subsequent anti-cancer therapy assessed by local reviewer will be reported.

During the study, CTs or MRIs and bone scans may be performed at any time in case of PSA progression, symptomatic progressive disease, change of anti-cancer therapy or if considered appropriate in the investigator's judgment. (Section 1.3). Such unscheduled imaging must be sent for central review and radiological progression assessment.

Tumor measurements and assessments of malignant soft tissue lesions (visceral lesions and malignant lymph nodes) will be based on RECIST 1.1 and, separately, malignant bone lesions are to be assessed in accord the PCWG3 criteria (Eisenhauer et al. 2009, Scher et al. 2016) (Appendix 9, Section 10.9 and Appendix 10, Section 10.10). Local site assessments are to be entered in the eCRFs and scans should be interpreted by the same radiologist/nuclear medicine physician/investigator. Any soft tissue lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a soft tissue lesion previously treated with radiotherapy has clearly progressed on the baseline/ screening scan, it can be considered as a measurable lesion.

For assessment of eligibility criterion of metastatic disease, baseline CT/MRI and bone scans must first be reviewed by a local qualified site physician to confirm presence of metastases before submitting the scans to central review to confirm eligibility. If the local qualified site physician detects metastases of only local lymph nodes (below aortic bifurcation), the scans should not be submitted to central review and participants should not be randomized. The presence or absence of visceral metastases at baseline will be assessed by central review to establish stratification of randomized participants. Tumor response assessments following baseline will be also performed by central review. If/when local review determines radiological progression has occurred, that finding must be confirmed by central review before response imaging is discontinued and study treatment is stopped.

Further guidance on the acquisition of CT/MRIs and bone scans as well as information on how to transmit image files to the imaging core laboratory will be provided in the Imaging Guidelines for this study. Further information on RECIST 1.1 criteria for assessment of soft

tissue lesions and on PCWG3 criteria for assessment of bone metastases is provided in Appendix 9, Section 10.9 and Appendix 10, Section 10.10 respectively.

For PSA related endpoints (please refer to Section 9.4.2.2 for definition of time to CRPC, time to PSA progression and PSA undetectable rates), PSA values obtained by central laboratory will be used.

For time to initiation of the subsequent anti-cancer therapy, all new anti-cancer therapies have to be reported with start date and reason to start.

Pain progression is defined as an increase of ≥ 2 points from baseline (day 1 score) in question 3 of BPI-SF (related to the worst pain in the last 24 hours) taken as a 7-day average. Pain will be assessed with the BPI-SF questionnaire (Appendix 7 in Section 10.7) during the visit, pain diary entries from 6 days preceding the visit and on the day of the visit from baseline until documented pain progression. The pain diary consists of 7copies of BPI-SF questionnaire. Initiation or change in the use of other non-opioid analgesics is not used in the analysis of pain progression.

For time to first prostate cancer-related invasive procedures, only procedures needed for alleviation of symptoms, signs or findings caused by progression in prostate will be collected until the first prostate-cancer invasive procedure occurs or change of anti-cancer treatment, whichever occurs first. See Section 9.4.2.3 for further explanations.

Analgesic 24–hour consumption log–eCRF should be collected on the same day as pain assessment questionnaires. Physician should record whether or not the participant has initiated opioid therapy since last visit and to record analgesic pain medications consumed by the participant over last 24 hours. To facilitate assessment of analgesic use, at each visit, participants should be requested to list all the pain medications consumed since the last visit, therefore based on the investigator's preference blister packs or written notes or any other applicable methods may be needed.

For all visits where questionnaires are administered either via electronic patient-reported outcome (ePRO) device, or paper forms, the questionnaires should be administered at the start of the visit prior to any study–related procedure or other clinical activities.

Survival status will be assessed until death or lost to follow-up. An additional survival sweep will be performed for primary analysis and prior to any subsequent analysis of OS.

8.2 Safety Assessments

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

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

In a potential state of pandemic, if the study participant is not able to come to the investigational site for protocol-specific visits, alternative methods for safety assessments (phone contact, virtual visit, alternative location for laboratory tests and imaging) could be implemented when necessary and feasible, to assure the safety of study participants. Darolutamide, typically distributed for self-administration, is also amenable to alternative secure delivery methods.

Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing information (e.g. for protocol-specified procedures). The specific information (e.g.

explanation of the basis of the missing data) will be captured in the case report form and the information will be summarized in the clinical study report. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

8.2.1 Physical Examinations

- A physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Neurological and Skin systems. Height (at Screening only) and weight will also be measured and recorded as outlined in the SoA (see Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Body temperature, heart rate, and blood pressure will be assessed as outlined in the SoA (see Section 1.3).
- Vital signs will be measured after 10 minutes of rest in supine position and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3 Electrocardiogram (ECG)

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT. The QTc intervals (QTcF by Fridericia formula and QTcB by Bazett formula) will be calculated by eCRF system.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
    - The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days (+7 days) (EOT visit) after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the protocol and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory are considered clinically significant by the

investigator, (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5 ECOG Performance Status

- An ECOG PS score of 0, 1 or 2 is required for study inclusion (see Section 5.1). During the study, assessment of ECOG PS is carried out as indicated in the SoA (Section 1.3).
- Grading definitions for ECOG PS are given in Table 8–1 below.

Table 8–1 Definitions for ECOG PS Grading

Grade	Description
0	Fully active, able to carry on all pre-diseases 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	Dead.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = Performance status

8.2.6 Population characteristics

8.2.6.1 Demographic

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

8.2.6.2 Medical history

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

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

Detailed instructions on the differentiation between medical history and AEs can be found in Section 10.3.

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. Prior radiotherapy on primary tumor and/or metastatic sites will be reported including the sites, the dose and date of completion of radiation.

8.2.6.3 Other baseline characteristics

Baseline characteristics relating to disease factors include:

- QoL assessment (FACT-P and BPI-SF)
- 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

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the signing of the informed consent form (ICF) until the EOT visit after 30 days (+7 days) since the last dose of the study drug as per the SoA (Section 1.3).

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

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

Medical occurrences that started or deteriorated after signing informed consent will be recorded as adverse events.

All SAEs must be immediately (within 24 hours of the investigator's awareness) reported to the sponsor or designee, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If the investigator learns of any SAE, at any time and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

In addition, during the Follow-up period participants will be followed for:

- Study drug-related SAEs
- Any anti-cancer treatment

8.3.2 Method of Detecting AEs and SAEs

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

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

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

Recurrence or disease progression should not be reported as AE/SAE. If there are separate identifiable clinical consequences that result from the disease progression (for example bone pain), the clinical consequence is to be reported as an AE/SAE.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. A follow-up report to an SAE should be prepared if any relevant change in the condition of the study participant occurs after the initial report. The follow-up report should be documented as an update to the initial report. A SAE follow-up form should be forwarded within 24 hours of the investigator's awareness and if the follow-up information changes the investigator's assessment of the causality, this should also be noted on the follow-up SAE form All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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

8.3.5 Pregnancy

Sexually active male participants must agree to use condoms as an effective barrier method and refrain from sperm donation, and/or their female partners of reproductive potential to use a method of effective birth control, during the study drug treatment and for 4 weeks after the last dose of the study treatment with darolutamide, (inclusion criterion).

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

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

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

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

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

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

8.3.6 Adverse Events of Special Interest

There are no adverse events of special interest.

8.4 Treatment of Overdose

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

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

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

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

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

In the event of an overdose, the investigator should:

1. Closely monitor the participant for any signs of toxicity and appropriate supportive treatment should be provided if clinically indicated.
2. Any overdose (intentional or accidental) or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF).
3. Adverse events associated with (or resulted from) an overdose or incorrect administration of study drug should be reported as Serious Adverse Event.

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

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

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Refer to Section 8.8 for pharmacodynamic biomarkers.

8.7 Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study if approved by local ECs / IRBs and competent authorities. See Section 8.8 for details.

Optional whole genome sequencing will be offered to all participants (not applicable for China). See Appendix 6 (Section 10.6) for details.

8.8 Biomarkers

- In this study, genetic as well as non-genetic biomarkers will be investigated. Genetic investigations may be of any kind, except for whole genome sequencing.
- **Timing** – see SoA (Section 1.3) for planned time points of sample collection.
- **Sample handling and storage** – Details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.
- **Medical history information** – If any additional molecular information about the tumor was collected in the course of treatment prior to entry of the participant in the study, the results may be collected in order to include this data in biomarker analyses.

- **Data analysis and Reporting** – 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.
- In exceptional circumstances, if permission for specific biomarker samples collection is not obtained from local authority, Chinese sites will be instructed not to collect these samples until permission is granted.

8.8.1 Potential Predictive Biomarkers

Biomarker status will be correlated with clinical outcome to explore whether any molecular characteristics appear to define participant populations that are particularly sensitive or resistant to darolutamide.

Plasma analysis:

Candidates of genes for the evaluation from circulating tumor deoxyribonucleic acid (ctDNA) are AR, phosphatase and tensin homolog (PTEN). The types of analyses may comprise the identification of mutations, gene amplifications or splice variants. Furthermore, the plasma samples may serve as source for non-coding microRNA, as possible markers describing treatment response. (For China, only analyses as granted by local authorities will be performed.)

Tumor biopsy analysis (not applicable for China):

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 that characterize molecular subtypes contributing to clinical benefit to therapy.

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 participant may benefit for further guidance. Note, however, that this is not considered to be mandatory by this study protocol.

Whole blood analysis (not applicable for China):

Biomarkers related to drug safety, efficacy, or mechanism of action may 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.

8.8.2 Pharmacodynamic Biomarkers

Pharmacodynamic biomarkers will be evaluated in samples collected before and during treatment in order to determine the impact of darolutamide on these biomarkers. Candidate markers will be analyzed from plasma samples to quantify various proteins of interest, to attempt to identify a protein signature that correlates with drug response, and/or assessment of variations in allelic fractions by analysis of ctDNA to investigate tumor evolution under treatment and potentially monitor treatment response. (For China, only analyses as granted by local authorities will be performed.)

8.8.3 Other Biomarkers (not applicable for China)

In addition to the biomarkers described above, further biomarkers related to, e.g., the mode of action or the safety of the study drug and similar drugs may be investigated. The same applies to further biomarkers deemed relevant to cancer and associated health problems. These investigations may include e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

Assuming a one-sided alpha of 0.025 for rPFS, a power of 90%, and a randomization ratio of 2:1 between the experimental and control arms, 214 events are required to detect a 60% increase in median time of rPFS (HR 0.625).

Assuming an exponential distribution of rPFS events and a control arm median time of 20 months, the active arm median would be approximately 32 months, which is a 60% increase in median time.

The expected study duration is approximately 36 months assuming approximately 665 participants are randomized at a rate of 45 participants per month, an enrollment ramp-up time of 6 months, approximately 18 months until randomization is complete, a dropout rate of 33% for rPFS follow-up, exponentially distributed event times, and 20-month median time of rPFS for the control group.

Assuming a 25% screening failure rate, approximately 886 screened participants would lead to 665 randomized participants.

9.3 Populations for Analyses

Populations for analyses are defined in Table 9–1.

Table 9–1 Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF.
Full Analysis Set (FAS)	All participants who were randomized are included in the Full Analysis Set. The participants in this set will be grouped according to the treatment they were allocated to receive at randomization, irrespective of actual treatment.
Safety analysis set (SAF)	All participants who were randomized and took at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received.

Abbreviations: ICF = Informed consent form

If there are participants who received the wrong study drug, safety data should be analyzed as treated. For example, if a placebo participant received at least one dose of the active test drug, this participant should be included in the test drug group for safety analysis. However, if a participant randomized to the test drug group received at least one dose of placebo and also at least one dose of test drug, this participant should be included in the test drug group. A participant should be included in the placebo group only if he received exclusively placebo (i.e. not any dose of test drug).

9.4 Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints for double-blinded phase.

The SAP which includes a more technical and detailed description of the statistical analyses described in this section will be developed and finalized before database release.

For any planned analyses for the open-label phase, a supplementary SAP will be developed.

9.4.1 General Considerations

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

9.4.2 Efficacy analyses

9.4.2.1 Primary Endpoint

The primary endpoint is **radiological progression-free survival (rPFS)** using conventional imaging method (^{99m}Tc-phosphonate bone scan, CT/MRI scan), assessed by central review based on RECIST v. 1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases. rPFS is defined as the time from the date of randomization to the date of first documentation of radiological progressive disease or death due to any cause, whichever occurs first. Additional definition details and censoring rules will be provided in the SAP.

Analysis of rPFS

All randomized participants (FAS) will be included in the primary analysis of rPFS by central review. The analysis will be performed when approximately 214 events of rPFS are observed. The primary analysis will be a stratified log–rank test with the same stratification factors as used for randomization (from IWRS).

The HR (darolutamide group/placebo) for rPFS and its 95% confidence interval will be calculated using the Cox model, stratified by the same factors as stated above. Kaplan–Meier (KM) estimates for rPFS will be presented for each treatment group. The KM estimates at time points such as 3 months, 6 months, etc., together with corresponding 95% confidence intervals (CIs) and the differences of these estimates between the darolutamide group and the placebo group will be presented.

The overall 1–sided type I error rate for the analysis of rPFS is 0.025. No interim analyses of rPFS are planned.

9.4.2.2 Secondary Endpoints

- **Overall survival (OS)** is planned to be a key secondary endpoint and is defined as the time from the date of randomization to the date of death from any cause.

Other secondary endpoints are:

- **Time to castration–resistant prostate cancer (CRPC)**, defined as the time from the date of randomization to the date of first castration resistant event (radiological progression, PSA progression or symptomatic skeletal events, whichever occurs first).
- **Time to initiation of subsequent anti-cancer therapy**, defined as the time from the date of randomization to initiation of first subsequent antineoplastic therapy for prostate cancer.
- **Time to PSA progression,** defined as the time from the date of randomization to the date of first PSA progression. Participants without PSA progression as of database cut–off, whether or not surviving, will be censored at the last total PSA laboratory assessment date.
  PSA progression is defined as a ≥25% increase above the nadir (lowest at or after 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.
- **PSA undetectable rates (<0.2 ng/mL),** defined as the percentage of participants with detectable PSA values (≥0.2 ng/mL) at baseline which become undetectable (<0.2 ng/mL) during the period between randomization and the earlier of 30 days after last dose of study drug or change of anti-cancer therapy.
- **Time to pain progression,** defined as the time from the date of randomization to pain progression, where progression is defined as an increase of 2 or more points from baseline in question 3 of the BPI-SF questionnaire related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores.
  For **asymptomatic** participants (worst pain subscale [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 points increase in WPS score) score from baseline observed at 2 consecutive evaluations ≥4 weeks apart.
  For **symptomatic** participants (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 points increase in WPS score) score from baseline observed at 2 consecutive evaluations ≥4 weeks apart and a WPS of ≥4.
Pain will be assessed with the BPI–SF questionnaire (Appendix 7, Section 10.7) during the visit, prior to any procedures or examination by physician. Participants who have not experienced pain progression at the time of analysis will be censored on the last date the participant was known to have not progressed. Participants with no on study assessment or no baseline assessment will be censored at the date of randomization.

Analysis of secondary endpoints

The secondary efficacy endpoints will be analyzed in the FAS population at the time of primary analysis unless otherwise specified in SAP. Time–to–event endpoints will be analyzed using same method as the primary efficacy variable. The stratified log–rank test with randomization stratification factors will be used to compare treatment effect. 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 will be specified in SAP.

Only overall survival will be tested at the final analysis time point, when the open-label phase is ended. Therefore, during the open-label period, data collection will continue with recording of survival status.

9.4.2.3 Other Pre-specified Endpoints

- **Progression-free survival 2 (PFS2)** as assessed by the investigator, is defined as the time from randomization to first occurrence of clinical, biochemical, or radiological disease progression under first subsequent anti-cancer therapy or death, whichever occurs first.
- **Time to symptomatic skeletal event (SSE)**, defined as the time from the date of randomization to the date of 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.
- **Biomarkers**. Analysis of biomarkers will be described in a separate analysis plan. (For China, only analyses as granted by local authorities will be performed.)
- **Time to deterioration in the Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P) total score**, is defined as the interval from the date of randomization to the first date a participant experiences a decrease of 10 points in the FACT-P total score. Symptoms and QoL will be assessed with the FACT-P questionnaire (Appendix 8, Section 10.8) during the visit, prior to any procedures or examination by physician.
- **Time to first prostate cancer-related invasive procedure** is defined as time from randomization to date of first prostate cancer-related invasive procedure.

  Prostate cancer-related invasive procedure is defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer

(e.g., catheterization of the bladder, percutaneous drainage of hydronephrosis, palliative electro resection of the prostate, etc.). Status of cancer-related invasive procedure will be assessed from randomization until the first cancer-related invasive procedure or change of anti-cancer therapy, whatever occurs first.

9.4.3 Safety Analyses

All safety analyses will be performed in the SAF population based on actual treatment received.

The safety variables include:

- TEAEs until the EOT visit
- TESAEs until the EOT visit
- Study drug–related TESAEs should be reported to sponsor regardless of the length of time from the study completion
- Physical examinations including weight
- Vital signs and body temperature: BP and heart rate (HR)
- 12–lead electrocardiogram (ECG)
- Clinical laboratory safety assessments (hematology, clinical chemistry, urinalysis)
- ECOG PS

Safety analysis

AE/SAE collection will start after signing the IC. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Descriptive summary tables will be presented on all safety parameters by treatment group. The safety assessment period for TEAE will start after the first dose of study drug until 30 days after the last treatment with darolutamide/placebo. Participants will be monitored for AEs using the NCI–CTCAE v. 5.0.

The AEs and safety laboratory parameters will be presented with their worst NCI–CTCAE v. 5.0 grade.

9.4.4 Other Analyses

The details of the analysis for the exploratory biomarker variables may be provided in the SAP or a separate Biomarker evaluation plan.

9.5 Interim Analyses

For this study no formal interim analysis for the primary endpoint is planned. At the time of primary analysis an interim analysis for secondary endpoint OS will be conducted. A second final OS analysis will be conducted later. Additional details regarding the statistical plan for the interim and final analysis of OS will be provided in the SAP.

9.6 Data Monitoring Committee (DMC) or other Review Board

An independent Data Monitoring Committee (DMC) will be instituted for this study in order to ensure ongoing safety of study participants. The DMC will conduct risk/benefit assessment during periodic data review meetings, and provide a formal recommendation for

continuation/termination of the study. The DMC will operate independently of the sponsor and investigators. The DMC will review safety data as per a separate DMC charter.

A Steering Committee including prostate cancer experts and oncologists, familiar with the existing treatment paradigm in mHSPC and are involved in current development research in this disease area will review, monitor and provide advice regarding the progress of the study in order to ensure alignment between the study conduct plan and the study protocol. Feedback from Steering Committee will be considered for the start of open-label phase, once primary analysis results are available.

Details on the responsibilities and operations of the DMC and Steering Committee will be provided in the respective committee charters.

10. Supporting Documentation and Operational Considerations

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

10.1.1 Regulatory and Ethical Considerations

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

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- Participants 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 participant.
- The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative (if acceptable by local law) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if acceptable per local law) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study as applicable.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

10.1.4 Data Protection

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

10.1.5 Committees Structure

For details see Section 9.6.

10.1.6 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 trials in participants are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug

trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers, participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

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

10.1.7 Data Quality Assurance

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

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Source Data Identification (SDI) Form.

10.1.9 Study and Site Start and Closure

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

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

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

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

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

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.

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

- 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.

10.1.10 Publication Policy

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- Investigators may publish or present individual study data (including case reports) obtained in the course of this study but only after the primary report and/or publication of the study results in their entirety. If publishing individual site data is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

10.2 Appendix 2: Clinical Laboratory Tests

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

Table 10–1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	The results of each test must be entered into the CRF.			

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

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, after providing written IC for participation in the study, may or may not be temporally associated with the use of study drug, whether or not considered related to the study drug.
- Treatment-emergent AE (TEAE) is defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant (e.g. requiring treatment intervention, study dose interruption/ discontinuation, dose reduction) in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

For efficacy studies, include:

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

For non-efficacy studies involving marketed products in established indications, include:

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be

Events Meeting the AE Definition
reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

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

10.3.2 Definition of SAE

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

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

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the CRO/sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the CRO/sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the CRO/sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated and transient in nature by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

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

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO/sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the cause of death with a copy of any

Follow-up of AEs and SAEs
post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to CRO/sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

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

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

10.4 Appendix 4: Participant Discontinuation

Participants must be discontinued from the study treatment in case of hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug. DILI should be suspected after other causes of liver injury have been excluded.

Criteria for study treatment discontinuation (FDA 2009):

- ALT or AST >8 x ULN

- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (TBL >2 x ULN or INR >1.5)
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

10.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance is specified in Section 5.1.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

10.6 Appendix 6: Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. See Section 8.8 for details.

Whole genome sequencing (WGS) will be offered to all participants. The WGS analysis will only be carried out in samples from those participants who have provided respective optional informed consent. Participants who do not wish to have their sample(s) analysed for WGS may still participate in the study (not applicable for China).

Details on sample handling will be provided separately.

10.7 Appendix 7: BPI-SF

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

Pt: _____

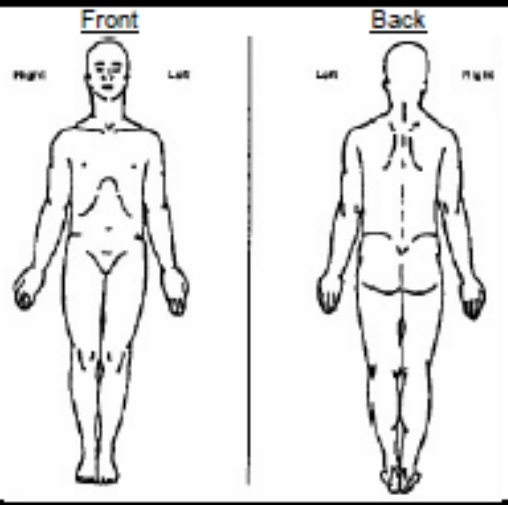
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials: _____

Study Subject #:

Study Name: _____

Protocol #: _____

Pt: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

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

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

10.8 Appendix 8: FACT-P (Version 4)

FACT-P (Version 4)

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 the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS2	I feel sad	0	1	2	3	4
GS22	I am satisfied with how I am coping with my illness	0	1	2	3	4
GS23	I am losing hope in the fight against my illness	0	1	2	3	4
GS24	I feel nervous	0	1	2	3	4
GS25	I worry about dying	0	1	2	3	4
GS26	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
H&N2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
H&N3	I am able to have and maintain an erection	0	1	2	3	4

10.9 Appendix 9: RECIST 1.1 Criteria

This study will use RECIST 1.1 criteria (Eisenhauer et al. 2009) for assessment of extra-skeletal malignant lesions. Metastatic bone lesions will be assessed in accord with PCWG3 criteria (Scher et al. 2016); see Appendix 10, Section 10.10).

RECIST 1.1 criteria:

Definition of Measurable disease:

- Soft tissue/ visceral tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan. If scans with slice thicknesses greater than 5 mm are used, the minimum size should be twice the slice thickness.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short axis* when assessed by CT scan (for CT scan slice thickness of 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease

All other lesions are considered non-measurable. This includes small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and also truly non-measurable lesions, such as: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung.

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment:

Bone lesions: (Note: not assessed by RECIST 1.1 in the current study)

- Lytic bone lesions, with an identifiable soft-tissue component, (e.g., lytic bone lesions in renal cell carcinoma) evaluated by CT or MRI can be considered as measurable lesions if the soft-tissue component otherwise meets the definition of measurability.
- Blastic bone lesions are considered as non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs

should be identified as target lesions and will be recorded and measured at baseline (this means in instances where participants have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the **baseline sum diameters**. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective change in the measurable dimension of the disease.

Optimally, lesions selected as target (measurable) lesions should not be biopsied. Additional guidance will be provided to the site on decisions about performing biopsies on potential target lesions when only one potential target lesion exists at baseline.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes (with short axis ≥ 10 mm and < 15 mm) not considered as target should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). Please note that some non-target lesions may actually be measurable, but if they were chosen to be followed as non-target lesions, they should be assessed only qualitatively. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Best Response: The best overall response for a participant is the best response recorded from the start of the study intervention until the end of treatment or Active Follow-up (A-FU), if applicable, taking into account any requirement for confirmation. The participant’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Complete Response (CR): Disappearance of all non-nodal target lesions. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of < 10 mm. In addition, there must be normalization of any applicable tumor marker.

Since lymph nodes are normal body structures, it is not expected that they disappear. Lymph nodes identified as target lesions should always have the short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a lymph node is defined as normal when having a short axis of < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study.

Non-CR/Non-PD (to be used for participants with non-target lesions only**)**: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions (see comments below), or the appearance of one or more new lesions, also constitutes progressive disease.

To achieve unequivocal progression in participants with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

In the absence of measurable disease, the same general concepts apply here as noted above.

The above text descriptions of the visit/time point response are logically equivalent to Table 10–2 below.

Table 10–2 RECIST 1.1 - Time Point Response for participants with target and non-target lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Time Point Response	Best Response for this category also requires
CR	CR	No	CR	-
CR	Non-CR/Non-PD	No	PR	-
CR	Not evaluated	No	PR	-
PR	Non-PD or not all evaluated	No	PR	-
SD	Non-PD or not all evaluated	No	SD	documented at least 6 weeks from treatment allocation
Not all evaluated	Non-PD	No	NE	-
PD	Any	Yes or No	PD	-
Any	PD	Yes or No	PD	-
Any	Any	Yes	PD	-

Abbreviations: CR = Complete response; NE = Not evaluated; PD = Progressive disease; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = Stable disease.

Participants with a global deterioration of health status requiring discontinuation of intervention without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of intervention.

Response duration

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented.

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease duration

Stable disease is measured from the start of the intervention until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

10.10 Appendix 10: Prostate Cancer Working Group 3 Criteria for Bone Metastases

In this study, the PCWG3 criteria will be used for bone metastases only. All extra-skeletal metastatic disease will be assessed by RECIST 1.1 (Appendix 9, Section 10.9).

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

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

^{99m}Tc-phophonate whole body planar bone scans are to be used for assessment of bone disease.

Bone lesion response types per PCWG3:

Bone scans will be used to assess that there are no new lesions (stable) or worse (new lesions)

Changes in intensity of uptake alone do not constitute progression or regression.

No new lesions would indicate continuation of therapy in the absence of other signs of progression (e.g., soft tissue progression by RECIST 1.1 above).

For new lesions and progression, the 2x2 rule is used: at least two new lesions on the first post-treatment scan, with at least two additional lesions on the next scan. If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan. For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan and confirmed on a subsequent scan [see Figure 2 in (Scher et al. 2016)] provide a confirmed progression status.

10.11 Appendix 11: Abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
A-FU	Active Follow-up
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ARi	Androgen receptor inhibitor
AST	Aspartate aminotransferase
$AUC_{0–24}$	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
BCRP	Breast Cancer Resistance Protein
BHA	Bone health agents
bid	Twice daily
BP	Blood pressure
BPI-SF	Brief Pain Inventory–Short Form
BT	Body temperature
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Declaration of Helsinki and Council for International Organizations of Medical Sciences
C_{max}	Maximum concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria For Adverse Events

ctDNA	Circulating tumor deoxyribonucleic acid
CYP	Cytochrome P450 enzyme
CYP3A4	Cytochrome P450 family 3 subfamily A member 4
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPD	1-diphosphonate
EBRT	External beam radiation therapy
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
e.g.	For example (exempli gratia)
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDP	Hydroxyethylene diphosphonate
HDPE	High density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMDP	Hydroxymethylene diphosphonate
HR	Heart rate
IB	Investigator’s Brochure
IC	Informed consent
ICECaP	Intermediate Clinical Endpoints in Cancer of the Prostate

ICF	Informed consent form
ICH	International Council for Harmonization
ID	Identification
i.e.	That is (id est)
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INN	International nonproprietary name
IRB	Independent Review Board
i.v.	Intravenous(ly)
IWRS	Interactive Web Response System
KM	Kaplan–Meier
LHRH	Luteinizing hormone-releasing hormone
MCH	Mean corpuscular hemoglobin
mCRPC	Metastatic castration-resistant prostate cancer
MCV	Mean corpuscular volume
MDP	Methylene diphosphonate
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
mHSPC	Metastatic hormone-sensitive prostate cancer
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute–Common Terminology Criteria for Adverse Events
NE	Not evaluated
NIMP	Non-investigational medicinal product
nmCRPC	Non-metastatic castration-resistant prostate cancer
OATP	Organic anion transporting polypeptide
OR	Odds ratio
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein

pH	Power of hydrogen
PI	Principal Investigator
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic(s)
PR	Partial response (except in Section 8.2.3)
PR	PR interval in ECG (in Section 8.2.3)
PS	Performance status
PSA	Prostate-specific antigen
PTEN	Phosphatase and tensin homolog
QoL	Quality of life
QRS	QRS interval in ECG
QT	QT interval in ECG
QTc	Corrected QT
QTcB	Corrected QT (Bazett's formulae)
QTcF	Corrected QT (Fridericia's formulae)
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
RNA	Ribonucleic acid
rPFS	Radiological progression-free survival
PFS2 as assessed by the investigator	Time from randomization to clinical, biochemical, or radiological disease progression under first subsequent anti-cancer therapy or death, whichever occurs first
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD	Stable disease
SDI Form	Source Data Identification Form
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SSE	Symptomatic skeletal event
SUSAR	Suspected unexpected serious adverse reaction
^{99m}Tc	Technetium 99m radionuclide

TEAE	Treatment-emergent adverse event
TMF	Trial Master File
UK	The United Kingdom
ULN	Upper limit of normal
US	The United States
USA	The United States of America
V1D1	Visit 1 Day 1
WBC	White blood cell
WGS	Whole genome sequencing
WPS	Worst pain subscale

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