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| **Document Type:** | Study protocol |
| **Official Title:** | A randomized, open-label, multicenter, phase 2b study to evaluate physical function, including balance and daily activity, in participants with castration-resistant prostate cancer treated with darolutamide or enzalutamide |
| **NCT Number:** | NCT04157088 |
| **Document Date:** | 06-Jun-2019 |

# Title Page

**Protocol Title:** A randomized, open-label, multicenter, Phase 2b study to evaluate physical function, including balance and daily activity, in participants with castration-resistant prostate cancer treated with darolutamide or enzalutamide

**Protocol Number:** 20609

**Compound Number:** BAY 1841788 (ODM-201)

**Study Phase:** Phase 2b

**Short Title:** DaroAcT: darolutamide physical function and daily activity study

**Acronym:** DaroAcT

**Sponsor Name:** Bayer HealthCare Pharmaceuticals Inc.

**Legal Registered Address:** Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA

**Regulatory Agency Identifier Number(s):** Not applicable

**Approval Date:** 06 JUN 2019

## Sponsor Signatory

PPD

PPD

PPD

Date

Medical Monitor Name and Contact Information will be provided separately.

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# 1. Protocol Summary

## 1.1 Synopsis

**Protocol Title:**

A randomized, open-label, multicenter, Phase 2b study to evaluate physical function, including balance and daily activity, in participants with castration-resistant prostate cancer treated with darolutamide or enzalutamide

**Short Title:**

DaroAcT: darolutamide physical function and daily activity study

**Rationale:**

There are multiple androgen receptor (AR) inhibitors indicated for prostate cancer with proven efficacy. However, these drugs are associated with adverse events including fatigue, cognitive dysfunctions, anorexia, sarcopenia, muscle weakness, and falls. There is an unmet medical need to improve patients' daily function, quality of life, and safety with an AR inhibitor with a better safety profile. Enzalutamide is the most frequently used AR inhibitor indicated for the treatment of patients with castration-resistant prostate cancer (CRPC).

The Phase 3 ARAMIS study of AR inhibitor darolutamide resulted in statistically significant improvement in metastasis-free survival compared to placebo (40.4 months vs. 22.0 months in the placebo arm) with a p-value of <0.001 and hazard ratio of 0.41 (95%CI: [0.34;0.50]). Treatment with darolutamide also resulted in a positive trend in overall survival and a delay in time to pain progression (Fizazi et al. 2019). The study also showed that darolutamide is well-tolerated and has a differentiated safety profile from other AR inhibitors (enzalutamide and apalutamide). However, currently there has not been a study to assess physical functioning and daily activities in patients treated with darolutamide.

The primary aim of this study is to evaluate the effects of treatment with darolutamide or enzalutamide on physical function as demonstrated by changes in balance, mobility, and cognitive function in participants with CRPC.

## Objectives and Endpoints:

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| The primary objective of this study is to compare the effects of treatment with darolutamide vs. enzalutamide on **physical function** as assessed by the Timed Up and Go (TUG) test in participants with castration-resistant prostate cancer. | Proportion of participants with a worsening in TUG time during the 24-week period from baseline. Worsening is defined as an increase of at least 1 second in TUG time from baseline. (The minimum clinically important difference [MCID] in TUG time is 1 second (Davies et al. 2016)) |
| **Secondary** | |
| The secondary objectives of this study are to:<br>• Compare the effects of treatment with darolutamide vs. enzalutamide on **physical function**, as assessed by the TUG test at 12 and 24 weeks, and by 52 weeks.<br>• Compare the effects of treatment with darolutamide vs. enzalutamide on **physical function** as assessed by Short Physical Performance Battery (SPPB) test at 12 and 24 weeks, and by 24 and 52 weeks.<br>• Assess the effects of treatment with darolutamide vs. enzalutamide on **daily activity** as assessed by accelerometry at 12 and 24 weeks, and by 24 and 52 weeks.<br>• Compare the effects of treatment with darolutamide vs. enzalutamide on **cognitive function** as assessed by Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), Controlled Oral Word Association (COWA), and Functional Assessment of Cancer Therapy – Cognitive questionnaire (FACT-Cog)<br>• Compare the effects of treatment with darolutamide vs. enzalutamide on **fatigue** as assessed by the Brief Fatigue Inventory (BFI)<br>• Compare the effects of treatment with darolutamide vs. enzalutamide on **depression** as assessed by the Patient Health Questionnaire-9 (PHQ-9)<br>• Evaluate **safety**, including adverse events (AEs) of interest, of participants treated with darolutamide vs. enzalutamide<br>  • Evaluate the effect of treatment with darolutamide or enzalutamide on prostate-specific antigen (PSA), survival status, and exposure | **Physical Function:**<br>• Proportion of participants with an increase of at least 1 second in TUG time at 12 and 24 weeks and during the 52 weeks from baseline.<br>• Time to worsening (increase of at least 1 second) in TUG time<br>• Proportion of participants with a worsening in SPPB total score at 12 and 24 weeks and during the 24 weeks and 52 weeks from baseline. Worsening is defined as a decline of at least 0.5 points in SPPB total score.<br>**Daily Activity:**<br>• Mean change from baseline in daily physical activity at 12 and 24 weeks, and during the 24 weeks and 52 weeks from baseline.<br>• Mean change from baseline in accelerometer-assessed proportion of time spent in light to vigorous physical activity based on a threshold of >100 activity counts per minute at 12 and 24 weeks, and during the 24 weeks and 52 weeks from baseline.<br>**Cognitive Function:**<br>• Proportion of participants with a decline in cognitive function during the 24 weeks and 52 weeks from baseline, as assessed by HVLT-R, TMT, and COWA. See Table 8–1 for the definition of decline for each test.<br>• Proportion of participants with a decline using a selected domain of FACT-Cog. Decline is defined as a decrease of >10 points during the 24 weeks and 52 weeks from baseline.<br>**Fatigue:**<br>• Proportion of participants with a worsening of fatigue during the 24 weeks and 52 weeks from baseline. Worsening is defined as an increase of at least 1 point in worst level of fatigue from baseline by 24 weeks and 52 weeks (based on item 3 of the BFI).<br>• Proportion of participants with an increase of at least 1 point in fatigue interference by 24 weeks and 52 weeks from baseline (based on items 4A-F of the BFI). |

| Objectives | Endpoints |
|---|---|
| | **Depression**:<br>• Proportion of participants with a worsening in scores in the PHQ-9 during the 24 weeks and 52 weeks from baseline. Worsening is defined as an increase of at least 1 point in worst level of depression from baseline by 24 weeks and 52 weeks.<br><br>**Safety**<br>• All treatment emergent AEs, SAEs, and AEs leading to study intervention discontinuation<br>• AEs of interest, including falls, fractures, and hypothyroidism<br><br>**Exposure and other:**<br>• Time to deterioration of KPS defined as at least a 10 point decline from baseline<br>• Treatment exposure of the study intervention including time on treatment<br>• Dose reductions of study intervention<br>• Time to PSA progression (as per Prostate Cancer Working Group [PCWG3] criteria)<br>• Survival status |

**Overall Design:**

This randomized, open-label, multicenter, Phase 2b study is designed to evaluate darolutamide therapy in participants with CRPC who have not previously been treated with apalutamide, darolutamide, or enzalutamide. CRPC patients with a history of treatment with abiraterone may be eligible if they have not progressed and discontinued treatment within 6 months before signing the ICF for this study.

The study consists of two phases, a lead-in phase and a randomized phase. In the lead-in phase, approximately 30 participants will be treated with darolutamide. Following the evaluation of the lead-in phase, approximately 120 additional participants will be randomized in a 1:1 ratio to receive either darolutamide (600 mg twice daily) or enzalutamide (160 mg once daily) in the randomized phase of the study. Randomization will be stratified by age (<75, ≥75 years).

The endpoints used in this study are novel in a way that decline in physical function will be evaluated using objective measures such as TUG, SPPB, and accelerometry, therefore, the lead-in phase has been added to be able to assess compliance and the variability of the endpoints and overall feasibility of the study execution. The randomized phase of the study will start only after the primary evaluation of the lead-in phase. Depending on the results of the lead-in phase, the primary endpoint of the study and/or sample size for the randomized phase may be changed.

The primary evaluation of the lead-in phase will occur when the last participant in the lead-in phase has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

**Disclosure Statement:**
This is an open-label treatment study consisting of a lead-in phase with one arm to be followed by a randomized phase with two arms.

**Number of Participants:**

- Lead-in phase: approximately 30 participants (darolutamide)
- Randomized phase: approximately 120 participants (1:1 darolutamide or enzalutamide)

**Intervention Groups and Duration:**
The following treatment arms are defined for this study:

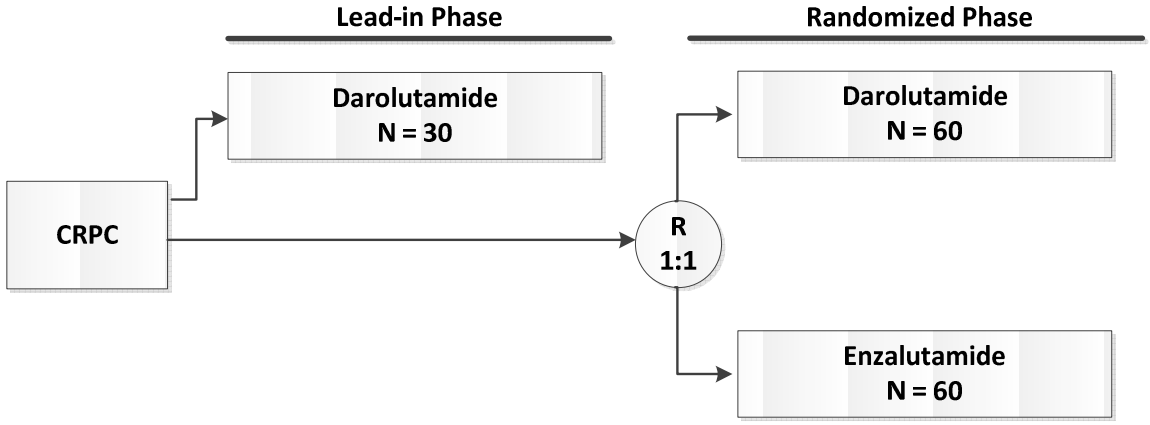
- Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equal to a total daily dose of 1200 mg
- Enzalutamide 160 mg (four 40 mg capsules) administered orally once daily. Capsules are to be swallowed whole. Enzalutamide can be taken with or without food.

All participants must continue to receive androgen deprivation therapy (ADT) of the investigator's choice (luteinizing hormone-releasing hormone [LHRH] agonist/antagonists) as standard therapy or have had orchiectomy.

**Data Monitoring Committee:** No

## 1.2 Schema

**Figure 1–1: Study Periods**




CRPC = castration-resistant prostate cancer; N = number of participants; R = randomization
Randomization will be stratified by age (<75 vs ≥75 years).

## 1.3 Schedule of Activities (SoA)

### 1.3.1 Lead-in phase

**Table 1–1 Schedule of Activities for the Lead-in Phase (darolutamide)**

| Assessment | Screening | Intervention + Observation Period | | | | | | | | End of treatment visit (30 days after last dose) [m] | Survival follow-up [l,n] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 1 Day 1 [i] | Week 4 [j] | Week 8 | Week 12 | Week 24 | Week 38 | Week 52 | from Week 53: Active follow up every 3 months [k,l] | | |
| **Time window allowed** | within 21 days prior to first dose | | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 14 days | ± 7 days | ± 1 month | + 1 month | ± 1 month |
| Informed consent | X | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | |
| Demography | X | | | | | | | | | | |
| Full physical examination including weight (height at screening only) | X | X | X | X | X | X | X | X | X | X | |
| Medical & surgical history including past and current medical conditions, substance use of drugs, alcohol, tobacco and caffeine. | X | | | | | | | | | | |
| Concomitant medication review | ←==========→ | | | | | | | | | | |
| Karnofsky Performance Scale | X | X | X | X | X | X | X | X | X | X | |
| Laboratory assessments (including liver chemistries) [a] | X | X | X | | X | X | X | X | X | X | |
| Serum PSA [a] | X | X | X | | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | |

**Table 1–1 Schedule of Activities for the Lead-in Phase (darolutamide)**

| Assessment | Screening | Intervention + Observation Period | | | | | | | | End of treatment visit (30 days after last dose) [m] | Survival follow-up [l,n] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 1 Day 1 [i] | Week 4 [j] | Week 8 | Week 12 | Week 24 | Week 38 | Week 52 | from Week 53: Active follow up every 3 months [k,l] | | |
| **Time window allowed** | within 21 days prior to first dose | | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 14 days | ± 7 days | ± 1 month | + 1 month | ± 1 month |
| Treatment dispensing / accountability | | X | ←==========→ | | | | | | | | |
| AE review [b] | ←==========→ | | | | | | | | | | |
| AEs of interest review, including fall [c] | ←==========→ | | | | | | | | | | |
| Timed Up and Go assessment (TUG) [d] | X [h] | X [h] | | | X | X | | X | X | | |
| Short Physical Performance Battery (SPPB) [d] | | X | | | X | X | | X | X | | |
| Accelerometry assessment [e] | X | | | | X | X | | X | X | | |
| Cognitive function [f] | | X | | | | X | | X | X | | |
| Brief Fatigue Inventory (BFI) [g] | | X | X | X | X | X | | X | | | |
| Patient Health Questionnaire (PHQ-9) | | X | X | X | X | X | | X | X | | |
| Survival status | | | | | | | | | | | X |

X = measure/action to be performed at the time point indicated
←=======→ = measure/action to be performed continually during the time period indicated

AE = adverse event; BFI = Brief Fatigue Inventory; COWA = Controlled Oral Word Association; CRF = case report form; HVLT-R = Hopkins Verbal Learning Test - Revised; PHQ-9 = Patient health questionnaire-9; PSA = prostate-specific antigen; SPPB = Short Physical Performance Battery; TMT = Trail Making Test; TUG = Timed Up and Go

a PSA will be assessed at the same time as other laboratory assessments. A time window of ± 14 days is allowed for laboratory and PSA assessments.
b Including survival, pain, radiographic progression, metastases, and skeletal events
c AEs of interest are fractures, falls, and hypothyroidism
d Physical function tests include SPPB and the TUG assessment.
e Accelerometry assessment will require the participant to wear an accelerometry device on the wrist or hip for a minimum of 7 days at each time point. The first accelerometry assessment is to be performed before the first dose (i.e. during screening).
f Cognitive function tests include the HVLT-R, TMT, and COWA, as well as the patient-reported outcome questionnaire FACT-Cog.
g BFI is a 5 minute self-assessment tool that identifies fatigue in cancer participants over a 24-hour period.
h The first TUG assessment is to be performed before the first dose (either during screening or Week 1 Day 1).
i Once the baseline procedures are completed, the first administration of study intervention will be provided at the study center and the participant will be provided with additional medication to take as scheduled through the Week 4 visit. (Each participant will be instructed to bring any remaining drug back to the center at the Week 4 visit.)
j At this and each subsequent visit, the participant will return dispensed but unused study intervention to the investigator for recording on the CRF. Reasons for non-compliance will be recorded. A new supply of study drug sufficient to meet the dosing requirements of each participant will be dispensed.
k Participants remaining on treatment beyond Week 52 will continue, where possible, to receive study intervention and assessments until the final evaluation of the randomized phase (i.e. at Week 52 for the last participant, see Section 4.4.1).
l Prior to the final evaluation of the randomized phase of the study, all participants will go into Week 53 active follow-up or survival follow-up as applicable.
m Each participant should complete an end of treatment visit after discontinuation of study intervention for any reason. All anti-cancer treatments after discontinuation of study intervention in this study will be recorded on the CRF at the end of treatment visit. See Section 4.4.2 for more details once the date of the final evaluation of the randomized phase is determined.
n Survival will be followed with contact with the participant and/or his caregiver every 3 months following the date of last treatment until the end of the study for participants treated with darolutamide (see Section 4.4.2).

### 1.3.2 Randomized phase

**Table 1–2 Schedule of Activities for the Randomized Phase (darolutamide, enzalutamide)**

| Assessment | Screening | Randomization | Intervention + Observation Period | | | | | | | | End of treatment visit (30 days after last dose) [n] | Survival follow-up [m,o] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 Day 1 [i] | Week 4 [k] | Week 8 | Week 12 | Week 24 | Week 38 | Week 52 | from Week 53: Active follow up every 3 months [l,m] | | |
| **Time window allowed** | within 21 days prior to randomization | | within 21 days after randomization | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 14 days | ± 7 days | ± 1 month | + 1 month | ± 1 month |
| Informed consent | X | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | |
| Full physical examination including weight (height at screening only) | X | | X | X | X | X | X | X | X | X | X | |
| Medical & surgical history including past and current medical conditions, substance use of drugs, alcohol, tobacco and caffeine. | X | | | | | | | | | | | |
| Concomitant medication review | ←==========→ | | | | | | | | | | | |
| Karnofsky Performance Scale | X | | X | X | X | X | X | X | X | X | X | |
| Laboratory assessments (including liver chemistries) [a] | X | | X [j] | X | | X | X | X | X | X | X | |
| Serum PSA [a] | X | | X [j] | X | | X | X | X | X | X | X | |
| Vital signs | X | | X | X | X | X | X | X | X | X | X | |

**Table 1–2 Schedule of Activities for the Randomized Phase (darolutamide, enzalutamide)**

| Assessment | Screening | Randomization | Intervention + Observation Period | | | | | | | | End of treatment visit (30 days after last dose) [n] | Survival follow-up [m,o] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 Day 1 [i] | Week 4 [k] | Week 8 | Week 12 | Week 24 | Week 38 | Week 52 | from Week 53: Active follow up every 3 months [l,m] | | |
| **Time window allowed** | within 21 days prior to randomization | | within 21 days after randomization | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 14 days | ± 7 days | ± 1 month | + 1 month | ± 1 month |
| Treatment dispensing / accountability | | | X | ←==========→ | | | | | | | | |
| AE review [b] | ←==========→ | | | | | | | | | | | |
| AEs of interest review, including fall [c] | ←==========→ | | | | | | | | | | | |
| Timed Up and Go assessment (TUG) [d] | X [h] | | X [h] | | | X | X | | X | X | | |
| Short Physical Performance Battery (SPPB) [d] | | | X | | | X | X | | X | X | | |
| Accelerometry assessment [e] | X | | | | | X | X | | X | X | | |
| Cognitive function [f] | | | X | | | | X | | X | X | | |
| Brief Fatigue Inventory (BFI) [g] | | | X | X | X | X | X | | X | | | |
| Patient Health Questionnaire (PHQ-9) | | | X | X | X | X | X | | X | X | | |
| Survival status | | | | | | | | | | | | X |

X = measure/action to be performed at the time point indicated
←=======→ = measure/action to be performed continually during the time period indicated

AE = adverse event; BFI = Brief Fatigue Inventory; COWA = Controlled Oral Word Association; CRF = case report form; HVLT-R = Hopkins Verbal Learning Test - Revised; PHQ-9 = Patient health questionnaire-9; PSA = prostate-specific antigen; SPPB = Short Physical Performance Battery; TMT = Trail Making Test; TUG = Timed Up and Go

a PSA will be assessed at the same time as other laboratory assessments. A time window of ± 14 days is allowed for laboratory and PSA assessments.
b Including survival, pain, radiographic progression, metastases, and skeletal events
c AEs of interest are fractures, falls, and hypothyroidism
d Physical function tests include SPPB and the TUG assessment.
e Accelerometry assessment will require the participant to wear an accelerometry device on the wrist or hip for a minimum of 7 days at each time point. The first accelerometry assessment is to be performed before the first dose (i.e. during screening).
f Cognitive function tests include the HVLT-R, TMT, and COWA, as well as the patient-reported outcome questionnaire FACT-Cog.
g BFI is a 5 minute self-assessment tool that identifies fatigue in cancer participants over a 24-hour period.
h The first TUG assessment is to be performed before the first dose (either during screening or Week 1 Day 1).
i Once the baseline procedures are completed, the first administration of study intervention will be provided at the study center and the participant will be provided with additional medication to take as scheduled through the Week 4 visit. (Each participant will be instructed to bring any remaining drug back to the center at the Week 4 visit.)
j Laboratory and PSA analyses and the physical examination will need to be repeated if they are not within 21 days from randomization. Week 1 Day 1 cannot be longer than 3 weeks from randomization.
k At this and each subsequent visit, the participant will return dispensed but unused study intervention to the investigator for recording on the CRF. Reasons for non-compliance will be recorded. A new supply of study drug sufficient to meet the dosing requirements of each participant will be dispensed.
l Participants remaining on treatment beyond Week 52 will continue, where possible, to receive study intervention and assessments until the final evaluation of the randomized phase (i.e. at Week 52 for the last participant, see Section 4.4.1).
m Prior to the final evaluation of the randomized phase of the study, all participants will go into Week 53 active follow-up or survival follow-up as applicable.
n Each participant should complete an end of treatment visit after discontinuation of study intervention for any reason. All anti-cancer treatments after discontinuation study intervention in this study will be recorded on the CRF at the end of treatment visit. See Section 4.4.2 for more details once the date of the final evaluation of the randomized phase is determined.
o Survival will be followed with contact with the participant and/or his caregiver every 3 months following the date of last treatment until the end of the study for participants treated with darolutamide, and until the final evaluation of the randomized phase for participants treated with enzalutamide (see Section 4.4.2).

# 2. Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death among men worldwide (World Health Organization 2017). It is the most common non-cutaneous cancer and the second leading cause of cancer-related deaths in men in Europe (World Health Organization 2008) and the United States (USA) (Hirsch et al. 2001). The most significant morbidity of prostate cancer is bone metastases.

## 2.1 Study Rationale

Most prostate cancer at diagnosis (in Europe and the USA) is localized disease. The majority of patients receive local treatment alone or with adjuvant androgen deprivation therapy (ADT). Many patients will eventually become resistant to ADT and develop castration-resistant prostate cancer (CRPC) (Dai et al. 2017). Contemporary research has led to the development of multiple active treatments for men with advanced disease, in addition to ADT. Management of CRPC involves the sequential use of these approaches, with the goals of prolonging survival and minimizing complications, but there is also a need to maintain quality of life.

There are multiple androgen receptor (AR) inhibitors indicated for prostate cancer with proven efficacy. However, these drugs are associated with adverse events including fatigue, cognitive dysfunctions, anorexia, sarcopenia, muscle weakness, and falls. There is an unmet medical need to improve patients' daily function, quality of life, and safety with an AR inhibitor with a better safety profile. Enzalutamide is the most frequently used AR inhibitor indicated for the treatment of patients with CRPC.

The Phase 3 ARAMIS study of AR inhibitor darolutamide showed clinically and statistically significant prolongation of time to metastasis in patients with non-metastatic CRPC treated with darolutamide as compared to placebo (Fizazi et al. 2019). The study also showed that darolutamide was well tolerated and has a differentiated safety profile from enzalutamide, which is why darolutamide-treated patients may have improved function for activities of daily living, less fatigue, and improved cognition. However, currently there has not been a study to assess physical function and daily activities in patients treated with darolutamide.

The primary aim of this study is to evaluate the effects of treatment with darolutamide or enzalutamide on physical function as demonstrated by changes in balance, mobility, and cognitive function in participants with CRPC. Standardized assessments of physical function including the Timed Up and Go (TUG) and Short Physical Performance Battery (SPPB) will be used to monitor participants' physical function on treatment (Belch et al. 2003). Each participant will also use an accelerometry device to track daily physical activity.

The cognitive function assessments included in this study are the Hopkins Verbal Learning Test, Revised (HVLT-R), Trail Making Test (TMT), Controlled Oral Word Association Test (COWA), and Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog). Fatigue and depression will be assessed using the Brief Fatigue Inventory (BFI) and Patient Health Questionnaire-9 (PHQ-9), respectively.

## 2.2 Background

Darolutamide (ODM-201/BAY 1841788) is a novel non-steroidal AR inhibitor that appears to negligibly cross the blood–brain barrier, reducing the occurrence of central side effects including seizures. Darolutamide has been found to block the activity of all tested/well-known mutant ARs in prostate cancer, including the recently identified clinically-relevant F876L

mutation that produces resistance to enzalutamide and apalutamide, and shows a higher binding affinity (9 nM) to AR compared with known second-generation antiandrogens and greater inhibitory efficacy (Eikelboom et al. 2017).

Darolutamide has been investigated in multiple Phase 1, 2, and 3 trials. Detailed information can be found in the Investigator's Brochure (IB).

The Phase 1/2 ARADES study in patients with metastatic CRPC showed tolerability of darolutamide in the population with advanced prostate cancer with metastatic lesions. The Phase 1 component of ARADES was an open-label, uncontrolled, non-randomized, multicenter, dose-escalation safety study with single- and multiple-dose pharmacokinetic (PK) evaluation in 24 patients. No dose-limiting toxic effects were reported and the maximum tolerated dose was not reached (Derry and Loke 2000).

The Phase 2 part of the trial randomized 124 patients to one of three darolutamide doses, with a primary endpoint of proportion of patients with PSA response (≥50% decrease in serum PSA) at Week 12. PSA response was achieved by 11 patients (29%) in the 200 mg group, 13 (33%) in the 400 mg group, and 11 (33%) in the 1400 mg group. The most common treatment-emergent adverse events (TEAEs) were fatigue or asthenia (12% of patients), hot flush (5%), and decreased appetite (4%) (Derry and Loke 2000).

The multinational, randomized, double-blind, placebo-controlled, Phase 3, efficacy and safety study of darolutamide in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS) met the primary endpoint of metastasis-free survival (MFS). In total, 1509 patients underwent randomization (955 to the darolutamide arm and 554 to the placebo arm). The median MFS was 40.4 months with darolutamide, as compared with 18.4 months with placebo (hazard ratio for metastasis or death in the darolutamide arm, 0.41; 95% confidence interval, 0.34 to 0.50; $p<0.001$). Darolutamide was also associated with benefits with regard to all secondary endpoints, including overall survival, time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event.

Darolutamide treatment was well-tolerated with comparable incidence of the most common TEAEs and similar incidence of permanent discontinuations of treatment between the darolutamide and the placebo arms. Incidences of TEAEs were below 10% in both treatment arms, with the exception of fatigue (12.1% darolutamide vs. 8.7% placebo) (Fizazi et al. 2019).

The median MFS with darolutamide in ARAMIS is similar to that in two other randomized controlled trials with enzalutamide and apalutamide in patients with non-metastatic CRPC. Median MFS was 36.6 months with enzalutamide (vs. 14.7 with placebo) in the PROSPER Phase 3 trial, and was 40.4 months with apalutamide (vs. 16.2 months with placebo) in the SPARTAN Phase 3 trial (Hussain et al. 2018, Smith et al. 2018). Rates of fatigue and asthenia, common adverse events for patients receiving hormone-targeted therapy for advanced prostate cancer, were lower in ARAMIS than in PROSPER and SPARTAN. In contrast to apalutamide and enzalutamide, darolutamide was not associated with increased rates of falls or fractures compared with placebo despite few patients using osteoclast-targeted therapies. Seizures were noted as a potential risk in the dose escalation and toxicity studies of enzalutamide (Scher et al. 2010). The incidence of seizure events was low and similar in the darolutamide and placebo arms; none of the patients with a medical history of seizure (12 in the darolutamide arm) experienced a seizure on study. Rates of rash and hypothyroidism, which were increased in patients receiving apalutamide compared with placebo, were low and similar between the darolutamide and placebo arms. Incidences of hypertension and central nervous system (CNS)-related adverse events were also low and similar between

darolutamide and placebo arms in ARAMIS. In PROSPER and SPARTAN, rates of hypertension and CNS-related adverse effects, such as mental impairment disorders and dizziness, were more common in patients receiving enzalutamide or apalutamide compared with placebo. The similar incidence of seizures, dizziness, and cognitive impairment in the darolutamide and placebo arms of ARAMIS may be linked to darolutamide's low blood–brain barrier penetration observed in preclinical studies (Zurth et al. 2018).

However, currently there has been no study to assess differences in physical function and the influence on quality of life of CRPC patients treated with these treatment options, and the effect of the treatments on daily function, quality of life, and activities are unknown. This study is designed to assess physical function, daily activity level, cognitive functions, and influence of secondary events in patients with CRPC treated with darolutamide and enzalutamide.

## 2.3 Benefit/Risk Assessment

The available clinical data suggest that darolutamide use is well-tolerated and safe for patients with non-metastatic CRPC. Darolutamide has been shown to significantly increase the time to metastasis compared to placebo while providing a favorable safety profile with low risk for adverse reactions that could deteriorate patients' quality of life. Therefore, the benefit from darolutamide treatment is significantly greater than the risk imposed by the treatment.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of darolutamide can be found in the IB. Information about the adverse events of enzalutamide is available in the prescription information of enzalutamide (XTANDI™ Prescribing information).

# 3. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| The primary objective of this study is to compare the effects of treatment with darolutamide vs. enzalutamide on **physical function** as assessed by the TUG test in participants with castration-resistant prostate cancer. | Proportion of participants with a worsening in TUG time during the 24-week period from baseline. Worsening is defined as an increase of at least 1 second in TUG time from baseline. (The MCID in TUG time is 1 second (Davies et al. 2016)) |
| **Secondary** | |
| The secondary objectives of this study are to:<br>• Compare the effects of treatment with darolutamide vs enzalutamide on **physical function**, as assessed by the TUG test at 12 and 24 weeks, and by 52 weeks.<br>• Compare the effects of treatment with darolutamide vs enzalutamide on **physical function** as assessed by the SPPB test at 12 and 24 weeks, and by 24 and 52 weeks.<br>• Assess the effects of treatment with darolutamide vs. enzalutamide on **daily activity** as assessed by accelerometry at 12 and 24 weeks, and by 24 and 52 weeks.<br>• Compare the effects of treatment with darolutamide versus enzalutamide on **cognitive function** as assessed by HVLT-R, TMT, COWA, and FACT-Cog<br>• Compare the effects of treatment with darolutamide versus enzalutamide on **fatigue** as assessed by the BFI<br>• Compare the effects of treatment with darolutamide vs. enzalutamide on **depression** as assessed by the PHQ-9<br>• Evaluate **safety**, including AEs of interest, of participants treated with darolutamide vs. enzalutamide<br>• Evaluate the effect of treatment with darolutamide or enzalutamide on PSA, survival status, and exposure | **Physical Function:**<br>• Proportion of participants with an increase of at least 1 second in TUG time at 12 and 24 weeks and during the 52 weeks from baseline.<br>• Time to worsening (increase of at least 1 second) in TUG time<br>• Proportion of participants with a worsening in SPPB total score at 12 and 24 weeks and during the 24 weeks and 52 weeks from baseline. Worsening is defined as a decline of at least 0.5 points in SPPB total score.<br>**Daily Activity:**<br>• Mean change from baseline in daily physical activity at 12 and 24 weeks, and during the 24 weeks and 52 weeks from baseline.<br>• Mean change from baseline in accelerometer-assessed proportion of time spent in light to vigorous physical activity based on a threshold of >100 activity counts per minute at 12 and 24 weeks, and during the 24 weeks and 52 weeks from baseline.<br>**Cognitive Function:**<br>• Proportion of participants with a decline in cognitive function during the 24 weeks and 52 weeks from baseline, as assessed by HVLT-R, TMT, and COWA. See Table 8–1 for the definition of decline for each test.<br>• Proportion of participants with a decline using a selected domain of FACT-Cog. Decline is defined as a decrease of >10 points during the 24 weeks and 52 weeks from baseline.<br>**Fatigue:**<br>• Proportion of participants with a worsening of fatigue during the 24 weeks and 52 weeks from baseline. Worsening is defined as an increase of at least 1 point in worst level of fatigue from baseline by 24 weeks and 52 weeks (based on item 3 of the BFI).<br>• Proportion of participants with an increase of at least 1 point in fatigue interference by 24 weeks and 52 weeks from baseline (based on items 4A-F of the BFI). |

| Objectives | Endpoints |
|---|---|
| | **Depression**:<br>• Proportion of participants with a worsening in scores in the PHQ-9 during the 24 weeks and 52 weeks from baseline. Worsening is defined as an increase of at least 1 point in worst level of depression from baseline by 24 weeks and 52 weeks.<br><br>**Safety**<br>• All treatment emergent AEs, SAEs, and AEs leading to discontinuation<br>• AEs of interest, including falls, fractures, and hypothyroidism<br><br>**Exposure and other:**<br>• Time to deterioration of KPS defined as at least a 10 point decline from baseline<br>• Treatment exposure of the study intervention including time on treatment<br>• Dose reductions of study intervention<br>• Time to PSA progression (as per PCWG3 criteria)<br>• Survival status |

# 4. Study Design

## 4.1 Overall Design

This is a randomized, open-label, multicenter, Phase 2b study to be conducted with a total of approximately 150 participants with CRPC who have not previously been treated with apalutamide, darolutamide, or enzalutamide. CRPC patients with a history of treatment with abiraterone may be eligible if they have not progressed and discontinued treatment within 6 months before signing the ICF for this study.

**The study consists of two phases, a lead-in phase and a randomized phase (see**

Figure 1–1). In the lead-in phase, approximately 30 participants will be treated with darolutamide. Following the primary evaluation of the lead-in phase, approximately 120 participants will be randomized in a 1:1 ratio to receive either darolutamide (600 mg twice daily) or enzalutamide (160 mg once daily) in the randomized phase of the study. Randomization will be stratified by age (<75, ≥75 years).

At the end of the lead-in phase of the study, the compliance and variability of the endpoints and overall feasibility of the study execution will be assessed. The randomized phase of the study will start only after the primary evaluation of the lead-in phase. Depending on the results of the evaluation, the primary endpoint for the randomized portion of the study may be changed. The final study design and endpoints for the randomized phase will be determined based on the lead-in cohort of 30 participants. The decision to move to the randomized phase of the study will involve reviewing the findings from the lead-in phase of the study with the members of the steering committee.

The primary evaluation of the lead-in phase will occur when at least 30 participants in the lead-in phase have been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. Additional participants may be enrolled in the lead-in phase if necessary.

The following endpoints will be evaluated at the end of the lead-in phase:

- the proportion of participants with a worsening in TUG time at week 12 and 24 and during the 24-week and 52-week period from baseline. Worsening is defined as an increase of at least 1 second in TUG time from baseline.
- the proportion of participants with a worsening in SPPB total score at week 12 and 24 and during the 24-week and 52-week period from baseline. Worsening is defined as a decline of at least 0.5 points in SPPB total score.
- the proportion of participants with a decline in cognitive function during the 24-week period from baseline, as assessed by HVLT-R and TMT

The suggested sample size for the randomized phase is based on the assessment of TUG test as the primary endpoint; however, after the feasibility assessment, the appropriate endpoint and the time point and time frame of evaluation of the endpoint for this part of the study will be chosen and the sample size will be reassessed.

The study is designed to evaluate physical function, including balance and daily activity, in participants treated with darolutamide or enzalutamide. It will also evaluate, safety, cognitive function, fatigue, and survival in participants treated with darolutamide or enzalutamide.

Participants will receive treatment (darolutamide or enzalutamide) until toxicity or disease progression and receive assessments during treatment. The study will continue until at least 52 weeks after the initial dose of the last participant, unless the participant discontinued due to lost to follow-up, withdrawal, or death. All participants will be followed up for survival status until the end of the study unless participants withdraw their informed consent.

The primary analysis for the lead-in phase will be performed when the last participant in the lead-in phase has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

The primary analysis for the randomized phase for the study will occur when last participant in the randomized phase of the study has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. A final analysis for the randomized phase for the study will occur when last participant in the randomized phase of the study has been on the study for at least 52 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

No data monitoring committee, dose escalation committee, or similar review group will be used for this study. The study will be conducted only in the USA at approximately 20 sites.

### 4.1.1 Randomization

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IWRS. The site will need to access the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form (CRF), if required. Randomization will be stratified by age (<75, ≥75 years).

## 4.2 Scientific Rationale for Study Design

This study is designed to assess physical function, daily activity level, cognitive functions, and influence of secondary events in participants with CRPC treated with darolutamide and enzalutamide. The primary aim of this study is to evaluate the effects of treatment with darolutamide or enzalutamide on physical function as demonstrated by changes in balance, mobility, and cognitive function in participants with CRPC. Standardized assessments of physical function including the TUG and SPPB will be used to monitor participants' physical function on treatment (Belch et al. 2003). Each participant will also use an accelerometry device to measure daily physical activity. The cognitive function assessments included in this study are the HVLT-R, TMT, COWA, and FACT-Cog. Fatigue and depression will be assessed using the BFI and PHQ-9, respectively. Before the randomized phase, in the lead-in phase in participants treated with darolutamide, these parameters will be assessed for feasibility and clinical relevance. After assessment in approximately 30 evaluable participants, the parameters and endpoints will be assessed and selected accordingly. This will allow a re-evaluation of the study design and endpoints before the randomized phase and allow a re-estimation of the assumptions for the comparator and study arms.

## 4.3 Justification for Dose

In the ARAMIS Phase 3 study, it was demonstrated that a dose of 600 mg darolutamide bid is sufficient to achieve maximum decrease in PSA and to result in a significantly longer metastasis-free survival (MFS) compared to the placebo arm. Overall, a darolutamide dose of 600 mg bid is considered to have an optimal benefit-risk profile.

The enzalutamide dose was based on approved dosing in the USA for enzalutamide in this population.

## 4.4 End of Study Definition

### 4.4.1 Final evaluation of the randomized phase

The final evaluation of the randomized phase will be at least 52 weeks from the initial dose of the study drug of the last participant randomized in the study, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

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.

### 4.4.2 End of assessments / follow-up

A participant is considered to have completed the study if he has completed all periods of the study including the last visit or evaluation at 52 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

For participants treated with darolutamide, at the time of the final evaluation of the randomized phase:

- If ongoing on study intervention, the participant can continue treatment until he meets the criteria for discontinuation (see Section 7). After discontinuation, the participant should complete an end-of-treatment visit and enter survival follow-up until the end of the study (defined in Section 4.4.3).
- If in survival follow-up, the participant can continue in survival follow-up until the end of the study (defined in Section 4.4.3).

For participants treated with enzalutamide, at the time of the final evaluation of the randomized phase:

- These participants should complete an end-of-treatment visit or a final survival follow-up, as applicable. All participants treated with enzalutamide will reach their final assessment. No data will be collected for participants treated with enzalutamide beyond this time.

### 4.4.3 End of study

The end of the study is defined as the time when the last participant treated with darolutamide has completed the end of treatment visit or survival follow-up; however, participants may continue darolutamide treatment outside of the study.

In the event a roll-over study is established:

- The last patient last visit (LPLV) date can be reached based on the last participant switching to a roll-over study or being switched to another drug supply.
- The present study will end when all participants have transitioned into the roll-over study or have discontinued from this study for another reason (e.g. consent withdrawn, lost to follow-up, death).
- Until the transition to a roll-over study, participants will continue to follow all the procedures and visits required in the current version of the protocol.

## 5. Study Population

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

### 5.1 Inclusion Criteria

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

**Age**

1. Participant must be 18 years of age inclusive or older at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2. Participants who have:
   - Histologically or cytologically confirmed adenocarcinoma of prostate, CRPC defined by disease progression despite ADT and may present as either a confirmed rise in serum PSA levels (as defined by PCWG3), the progression of pre-existing disease, and/or the appearance of new metastases. Metastatic and non-metastatic CRPC patients will be eligible.
   - KPS performance status of ≥80
   - Blood counts at screening: hemoglobin ≥9.0 g/dL, absolute neutrophil count ≥1500/µL, platelet count ≥100,000/µL
   - Screening values of serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN), total bilirubin ≤1.5 × ULN, creatinine ≤2.0 × ULN
   - Life expectancy of at least 1 year

- Eligible for treatment with enzalutamide (only for the randomized phase)

**Sex**

3. Male

   Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   Sexually active participants, unless surgically sterile, must agree to use condoms as an effective barrier method and refrain from sperm donation during study treatment and for 3 months after the end of the study treatment. Participants who are sexually active with a female partner of childbearing potential, unless surgically sterile, must agree to ensure that an additional form of contraception is also used. See Appendix 4 (Section 10.4) for contraceptive guidance for women of childbearing potential.

**Informed Consent**

4. 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 informed consent form (ICF) and in this protocol

## 5.2 Exclusion Criteria

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

**Medical Conditions**

1. Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis with abnormal renal function due to prostate cancer. Participants with visceral metastasis will be excluded.
2. Severe or uncontrolled concurrent disease, infection, or comorbidity
3. Past (within 6 months before the start of study intervention) or concurrent stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and/or congestive heart failure (New York Heart Association Class III or IV)
4. Uncontrolled clinically significant hypertension
5. Prior malignancy. Adequately treated basal cell or squamous cell carcinoma of the skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e. pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed 3 years before the start of study intervention and from which the participant has been disease free
6. Known metastatic brain or meningeal tumors
7. Prior or concurrent central nervous system disease, such as epilepsy, Parkinson's disease, Alzheimer's disease, dementia, or multiple sclerosis
8. Active viral hepatitis, active human immunodeficiency virus (HIV), or chronic liver disease
9. Gastrointestinal disorder or procedure that is expected to interfere significantly with absorption of study treatment
10. Major surgical procedure or significant traumatic injury within 28 days before the start of study intervention

11. Seizure disorder requiring medication
12. Non-healing wound, ulcer, or bone fracture
13. Substance abuse, medical, psychological, or social conditions that may interfere with the participant's participation in the study or evaluation of the study results
14. Non-ambulatory participants who need a wheelchair. Other assistive devices (e.g., cane or walker) are permitted.
15. Any illness or medical condition that is unstable or could jeopardize the safety of the participant and his compliance in the study
16. Clinically significant limitations in cognitive function and/or physical function, such as >20 seconds in the TUG assessment

**Prior/Concomitant Therapy**

17. Prior treatment with any of the following:
    - Second-generation AR inhibitors, such as enzalutamide, apalutamide, or darolutamide
    - Other investigational AR inhibitors
    - Progression on abiraterone acetate and discontinuation within 6 months before signing the ICF for the study
    - For mCRPC participants: any chemotherapy, and/or >2 prior lines of systemic anticancer treatment. Treatment with an LHRH agonist, LHRH antagonists, or orchidectomy is not counted as systemic treatment with regard to this exclusion criterion.
18. Use of estrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before the start of study intervention and AR inhibitors (bicalutamide, flutamide, nilutamide, cyproterone acetate) within 28 days before screening
19. Use of immunotherapy within 28 days before the start of study intervention
20. Treatment with radiotherapy/radiopharmaceuticals within 12 weeks before the start of study intervention
21. Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before the start of study intervention
22. Acute toxicities of prior treatments and procedures not resolved to grade ≤1 or baseline before the start of study intervention

**Prior/Concurrent Clinical Study Experience**

23. Previous participation in other clinical studies within 28 days before the start of study treatment or 5 half-lives of the investigational treatment of the previous study, whichever is longer

**Diagnostic assessments**

24. Known hypersensitivity to any of the study interventions, study drug classes, or excipients in the formulation
25. Inability to swallow oral medications

**Other Exclusions**

26. If, in the opinion of the investigator, the participant is unable to complete the different tests required for the study.

### 5.3 Lifestyle Considerations

No restrictions are required.

### 5.4 Screen Failures

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

During the screening period, if a participant has failed a test, the test may be repeated if the investigator has determined that the repeated screening test does not expose the participant to an unjustifiable health risk. The participant may be eligible for study participation if the repeated test meets the screening criteria and protocol window.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A participant who is rescreened is required to sign another ICF.

## 6. Study Intervention

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

### 6.1 Study Intervention(s) Administered

| Intervention Name | Darolutamide | Enzalutamide |
|---|---|---|
| Type | drug | drug |
| Dose formulation | film-coated tablet | soft tablet |
| Unit dose strengths | 300 mg | 40 mg |
| Dosage Level | 600 mg twice daily | 160 mg once daily |
| Route of administration | oral | oral |
| investigational medicinal product (IMP) / non- investigational medicinal product (NIMP) | IMP | IMP |
| Sourcing | Provided centrally by the sponsor | Commercially available |
| Packaging and Labeling | Will be provided in white opaque wide-necked high density polyethylene (HDPE) bottles closed with white opaque screw cap polypropylene (PP) / PP with seal polyethylene child-resistant. Each container will be labeled as required per country requirement. | Will be supplied via prescription for those in the enzalutamide arm as commercially available from the pharmacy and will not be supplied by the sponsor. |
| Current/Former Name(s) or Alias(es) | Darolutamide (BAY 1841788 / ODM-201) | Enzalutamide (Xtandi®) |

### 6.1.1 Medical Devices

All enrolled participants will perform accelerometry assessments as described in the SoA (Section 1.3). Additional accelerometry details will be specified in a separate Operational Site User manual.

1. Accelerometry medical devices (not manufactured by or for the sponsor) are provided for use in this study.
2. Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

## 6.2 Preparation/Handling/Storage/Accountability

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

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention 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 intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions will be made available to sites as required.

## 6.3 Measures to Minimize Bias: Randomization

This is an open-label study; however, all participants in the randomized phase will be centrally assigned to randomized study intervention 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.

The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment in the participant's source documents and on the applicable case report form, if required. Potential bias will be reduced by central randomization.

## 6.4 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc. The participant should be asked about the reason for obvious non-compliance. Deviation(s) from the prescribed dosage regimen should be recorded in the source records and eCRF.

## 6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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.

All participants must continue to receive ADT of the investigator's choice (LHRH agonist/antagonists) as standard therapy or have had orchiectomy. Switching ADT to an LHRH antagonist is permitted during study treatment.

All concomitant treatments must be recorded in the participant's source documents and on the CRFs, from the time of informed consent until the end of treatment visit at the time points specified in the SoA (Section 1.3). Once the participant has been withdrawn from treatment with the study intervention, subsequent systemic antineoplastic therapies for prostate cancer also will be recorded.

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

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. Concomitant short-term use is allowed.

Administration of 600 mg darolutamide bid over 4 days prior to administration of a single dose of 5 mg rosuvastatin, a BCRP substrate, together with food resulted in a 5.2-fold increase in mean exposure [AUC(0–24)] of rosuvastatin and a 4.9-fold increase in Cmax. These results indicate that co–administration of darolutamide can also increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, participants should be closely monitored for signs and symptoms of increased exposure to BCRP substrates. Dose modification of BCRP substrates should be considered based on the prescriber information.

For participants receiving enzalutamide in the study, the use of concomitant medications should follow the prescriber information for enzalutamide (XTANDI™ Prescribing information).

**Prohibited concomitant medications and treatments**

Concomitant treatment with another systemic antineoplastic therapy or another investigational medicinal product is prohibited with the exception of ADT throughout the study.

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

- any investigational medicinal product

- radiopharmaceuticals
- radium-223
- immunotherapy (e.g. sipuleucel–T)
- cytotoxic chemotherapy
- apalutamide, bicalutamide, flutamide, nilutamide
- abiraterone acetate, TAK–700, or other CYP17 inhibitors
- systemic ketoconazole as antineoplastic treatment for prostate cancer
- ADT switch to LHRH agonist
- another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study intervention
- any medication that would affect the assessment of physical or cognitive function

For prohibited prior therapy, please refer to the exclusion criteria in Section 5.2.

## 6.6 Dose Modification

In case a dose reduction is necessary, the study intervention will be administered as described in the following sections.

The dose or dosing schedule of the study intervention may be modified following the occurrence of clinically significant AEs.

### 6.6.1 Definitions

- **Delay**: Administration of study intervention is later than the planned schedule; however, no planned doses of medication are actually missed. Delays can only occur in regimens with a drug holiday, or regimens consisting of individual doses. Dose delay does not apply to the first administration of drug at the start of the study.
- **Interruption**: Unscheduled break in administration during which scheduled doses of study intervention are not received.

### 6.6.2 Dose modifications

Doses of study intervention may be interrupted or reduced in case of clinically significant toxicities that are related to study treatment. All dose modifications regardless of relatedness should be recorded on the CRF.

Study intervention may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study intervention within 28 days of the interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant's study record.

**Darolutamide**

A participant who experiences a darolutamide treatment-related grade 3 or 4 AE should interrupt study treatment until the AE improves to grade 2 or less. Darolutamide treatment is then to be restarted at 300 mg bid.

Additional details are provided in Table 6–1.

**Table 6–1 Dose Interruption and/or Reduction for Toxicities Considered Related to Darolutamide Treatment**

| Severity grade (NCI-CTCAE v 5.0) | Dose modifications | Permanent discontinuation of darolutamide |
|---|---|---|
| Grade 0-2 | Treat on time.<br>Per investigator's decision to interrupt or reduce darolutamide [a,b] | - |
| Grade 3 or 4 | Interrupt until grade ≤2 [a]<br>When the severity is grade ≤2, restart at a reduced dose of 300 mg bid [b,c] | If the dosing of the study intervention is temporarily or permanently reduced to 300 mg bid and a grade 3 or higher treatment-related AE occurs while the participant is on a dose of 300 mg bid, the participant must be withdrawn from treatment with darolutamide. |

Excludes clinically non-significant and asymptomatic laboratory abnormalities
AE = adverse event; bid = twice daily; NCI-CTCAE v 5.0 = National Cancer Institute - Common Terminology Criteria for Adverse Events version 5.0

a If darolutamide is interrupted for 28 consecutive days, darolutamide should be permanently discontinued.
b When the AE improves or is resolved, dose escalation to 600 mg bid may be considered at the discretion of the investigator.
c If the dose is re-escalated to 600 mg and any treatment-related AE with a severity grade 3 or higher occurs, a permanent dose reduction is required. A third occurrence of a grade 3 or higher treatment-related AE requires permanent discontinuation of darolutamide.

**Enzalutamide**

Dose modification and/or interruption for toxicities considered related to enzalutamide treatment can be made according to the prescription information (XTANDI™ Prescribing information). If a participant experiences a grade ≥3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to grade ≤2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

### 6.6.3 Dose reduction

**Darolutamide**

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

Dosing of darolutamide below 300 mg bid is not allowed. If a grade 3 or higher treatment-related AE occurs while the participant is on 300 mg bid, the participant must be withdrawn from darolutamide.

When an AE leading to dose reduction improves or is resolved, dose re-escalation to 600 mg bid may be considered at the discretion of the investigator.

**Enzalutamide**

Dose reduction of enzalutamide can be done according to the prescription information (XTANDI™ Prescribing information). The medical monitor must be notified of any dose reduction.

When an AE leading to dose reduction improves or is resolved, dose re-escalation may be considered at the discretion of the investigator.

### 6.6.4 Dose interruption

Participants should restart study intervention within 7 days of dose interruption, but the maximum time allowed for a dose interruption period is 28 consecutive days. Any participant requiring treatment interruption >28 consecutive days must be withdrawn from study intervention.

## 6.7 Intervention after the End of the Study

The study will continue until at least 52 weeks from the initial dose of the study intervention of the last participant randomized in the study, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

All anti-cancer treatments after discontinuation of treatment with study intervention in this study will be recorded on the CRF.

At the end of study intervention for the individual participant, further therapy is at the discretion of the investigator. Participants treated with darolutamide who are clinically benefitting can continue to receive treatment.

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

a) the study is terminated due to safety concerns

b) the participant can obtain medication used in this study as treatment from a government sponsored or private health program

# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

Participants will be followed up for survival status unless they withdraw their informed consent.

Participants will continue study intervention until intolerable toxicity or progressive disease.

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

## 7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for 52 weeks.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

## 7.2 Participant Discontinuation/Withdrawal from the Study

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

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

# 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 intervention.
- 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 participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

## 8.1 Efficacy Assessments

Assessments specific to tumor burden will not be collected in this study. Participants will be followed for survival to assess the 1-year survival rate.

## 8.2 Safety Assessments

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

Safety assessments in this study are AEs, as recorded by the investigator. Descriptive summary tables will be presented for all safety parameters by each treatment arm.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and graded using NCI-CTCAE version 5.0. A TEAE is defined as any event arising or worsening after start of study drug administration until 30 days after the last study drug intake.

Fatigue, cognitive function and depression will be assessed as described below.

Other AEs of interest including fractures, falls, fractures, and hypothyroidism will be collected with specific questions on CRF.

Study assessments for physical ability and cognitive function are described in Table 8–1.

**Table 8–1: Study Assessments for Physical Ability and Cognitive Function**

| Test | Description | Possible range of score | MCID / RCI from baseline |
|---|---|---|---|
| **Physical ability tests** | | | |
| **Timed Up & Go (TUG)** | The TUG test is used to assess a person's mobility and requires both static and dynamic balance. It uses the time that a person takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down.<br>Where possible, TUG time is to be measured by independent blinded assessors. | >1second | 1 second<br>(Davies et al. 2016) |
| **Short Physical Performance Battery (SPPB)** | The SPPB is a group of measures that combines the results of the gait speed, chair stand and balance tests. | 0–12 points | 0.5 points<br>(Davies et al. 2016) |
| **Cognitive Tests** | | | |
| **Hopkins Verbal Learning Test-Revised Total Recall (HVLT-R TR)** | The HVLT-R is a learning and memory test, in which the participant is asked to learn and recall a list of 12 words over 3 trials. | 0–36 words | ±5 words<br>(Wefel et al. 2011) |
| **Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR)** | Spontaneous recall is assessed before and after a delay. | 0–12 words | ±3 words<br>(Wefel et al. 2011) |
| **Hopkins Verbal Learning Test-Revised Delayed Recognition (HVLT-R RECOG)** | Recognition discriminability is also assessed after a delay. Four alternate versions of the test are used to minimize practice effects over time. | -12–+12 words | ±2 words<br>(Wefel et al. 2011) |
| **Trail Making Test (TMT)**<br>**Part A (TMTA)**<br>**Part B (TMTB)** | The TMT Part A (TMTA) assesses visual scanning and motor tracking requiring focused attention. Participants are required to sequentially connect numbered dots in ascending order that are randomly scattered across the test page.<br>Part B (TMTB) includes a divided attention component requiring mental flexibility (i.e., executive function). On this subtest, dots with numbers and | 1–2750 seconds<br>1–3750 seconds | ±12 seconds<br>±26 seconds<br>(Wefel et al. 2011) |

| Test | Description | Possible range of score | MCID / RCI from baseline |
|---|---|---|---|
| | letters are randomly scattered on the test page. Participants are required to alternate between connecting numbers and letters in an ascending sequential order.<br>Both tests require the participants to complete the sequence as fast as possible. TMTA is discontinued after 3 minutes and TMTB is discontinued after 5 minutes for participants who have difficulty in order to reduce participant burden. | | |
| **Controlled Oral Word Association (COWA)** | The COWA test assesses lexical fluency. Given a specific letter of the alphabet, participants are required to produce as many words as possible that begin with that letter. There are two alternate forms of the COWA, each with three unique letter exemplars. | 0 – unlimited words | ±12 words (Wefel et al. 2011) |
| **Cognitive tests – Patient-reported outcomes** | | | |
| **Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog)** | The FACT-Cog questionnaire was developed to assess perceived cognitive function and impact on quality of life (QOL) in cancer patients. It is a patient-reported outcome measure used to assess cognitive function in patients undergoing cancer therapy. | 0–28 points | 6.9-10.6 points (Cheung et al. 2014, Costa et al. 2018) |

COWA = Controlled Oral Word Association; FACT-Cog = Functional Assessment of Cancer Therapy-Cognitive; HVLT-R DR = Hopkins Verbal Learning Test-Revised Delayed Recall; HVLT-R RECOG = Hopkins Verbal Learning Test-Revised Delayed Recognition; HVLT-R TR = Hopkins Verbal Learning Test-Revised Total Recall; MCID = minimal clinically important difference; QOL = quality of life; RCI = reliable change index; SPPB = Short Physical Performance Battery; TMTA/TMTB = Trail Making Test Part A/B; TUG = Timed up & Go

In addition, fatigue will be assessed using BFI. BFI is a validated tool and consists of three questions assessing the severity of fatigue and six questions assessing the impact of fatigue on the participant's mood, social functioning and physical functioning. The BFI is a 9-item scale developed to assess subjective fatigue. Each question is asked in relation to the last 24 hours and is scored on an 11-point numerical rating scale, with higher scores indicating greater fatigue and interference with functionality. The first three questions measure fatigue severity at current, usual, and worst levels from 0 to 10, with 0 indicating "no fatigue," and 10 indicating "as bad as you can imagine". The following six questions assess fatigue interference with daily activities including general activity, mood, walking ability, normal work (both inside and outside the home), relations with other people, and enjoyment of life. Response options range from 0 to 10 with 0 indicating "does not interfere" and 10 indicating "completely interferes." Higher scores on the BFI correspond to greater self-reported levels of fatigue.

Depression will be assessed using PHQ-9. It is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument for common mental

disorders. The PHQ-9 is the depression module, which scores each of the 9 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria as "0" (not at all) to "3" (nearly every day) (Kroenke et al. 2001). As a severity measure, the PHQ-9 score can range from 0 to 27, since each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day). Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. Other depression is diagnosed if 2, 3, or 4 depressive symptoms have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. One of the 9 symptom criteria ("thoughts that you would be better off dead or of hurting yourself in some way") counts if present at all, regardless of duration.

### 8.2.1 Physical Examinations

A complete routine physical examination will be conducted at the time points outlined in the SoA (Section 1.3). Height (only baseline) and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.2 Vital Signs

Vital signs will be measured and will include temperature, systolic and diastolic blood pressure, and pulse.

### 8.2.3 Clinical Safety Laboratory Assessments

The laboratory safety assessments will be performed at the time points outlined in the SoA (Section 1.3).

Laboratory values will be classified by NCI-CTCAE severity grade.

Additional or repeated laboratory safety assessments may also be obtained according to the investigator's judgment.

- 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 relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory are considered clinically significant by the investigator, then these also need to be reported as SAE or AE.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - 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 laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

## 8.3 Adverse Events and Serious Adverse Events

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

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

If a participant experiences several study intervention-related toxicities with different grading, the recommendation of the worst grading should be used.

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE (Section 10.3.2).

The study intervention action should be recorded as detailed in the CRF.

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

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

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

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

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

An AE (irrespective of causal relationship) not completely resolved at the end of the pre-defined collection period must be followed up until resolution (defined as chronicity, baseline grade or complete resolution) or until the investigator considers the event will not improve further.

All SAEs will be collected from the signing of the informed consent form (ICF) until 30 days after the last dose, at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit(s) at the time points specified in the SoA (Section 1.3).

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the CRF.

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

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

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

### 8.3.2 Method of Detecting AEs and SAEs

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

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

### 8.3.3 Follow-up of AEs and SAEs

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

### 8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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 an 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.3.5 Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until at least 30 days after the last dose.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable. For details on AEs and SAEs, refer to Section 10.3.

## 8.4 Treatment of Overdose

**Darolutamide**

For this study, any dose of darolutamide greater than 600 mg (2 tablets of 300 mg) twice daily within a 24-hour time period will be considered an overdose.

The highest dose of darolutamide studied clinically was 900 mg twice daily, equal 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.

Therefore, in the event of intake of a higher than recommended dose, it is suggested that darolutamide treatment be continued with the next dose as scheduled.

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

**Enzalutamide**

For detailed guidance on overdosing please refer to the prescribing information for enzalutamide (XTANDI™ Prescribing information).

**In the event of an overdose of study intervention**

In the event of an overdose, the investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
2. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
3. Any overdose or incorrect administration of study drug should be noted in the participant's source documents and on the Study Drug Administration eCRF.

4. AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF.

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

### 8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

### 8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

### 8.7 Genetics

Genetics are not evaluated in this study.

### 8.8 Biomarkers

Biomarkers are not evaluated in this study.

### 8.9 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

There is no formal statistical hypothesis testing for the lead-in part of the study.

For the randomized portion of the study, this study will test the null hypothesis of no difference in the proportion of participants with a worsening in physical function as assessed by the TUG test in the two arms against the alternative hypothesis that there is a difference.

### 9.2 Sample Size Determination

**Lead-in phase**

Approximately 30 participants will receive study intervention in the lead-in phase of the study. The example point estimates of decline rates (physical or cognitive function) and the corresponding 2-sided 95% CI (based on exact binomial distribution) are shown in Table 9–1. For instance, decline/worsening for TUG test is defined as an increase of at least 1 second in TUG time from baseline. The definition of decline in cognitive functions is provided in Section 9.4.2. The values are provided as a reference rather than a basis for decision making.

**Table 9–1: Estimated Decline Rates and 2-sided 95% Confidence Intervals**

| | | 95% CI | | |
|---|---|---|---|---|
| **Number of participants with a decline** | **Observed Decline Rate** | **Lower limit** | **Upper Limit** | **Width (%)** |
| 0 | 0 | 0.00 | 11.57 | 11.57 |
| 6 | 20% | 7.71 | 38.57 | 30.85 |
| 12 | 40% | 22.66 | 59.40 | 36.74 |
| 18 | 60% | 40.60 | 77.34 | 36.74 |
| 24 | 80% | 61.43 | 92.29 | 30.85 |
| 30 | 100% | 88.43 | 100.00 | 11.57 |

CI: confidence interval

**Randomized phase**

The sample size calculation for the randomized phase of the study is based on the primary endpoint of physical decline (using TUG test as an example). In the event that the primary endpoint or the assumed rate of decline changes based on results from the lead-in phase of the study, the sample size will be adjusted accordingly.

Approximately 120 participants in the randomized phase of the study will provide 85% power to detect a difference of 20% in the two arms using one-sided alpha of 10%. This is assuming that 20% of participants in the darolutamide arm and 40% of participants in the enzalutamide arm will have a worsening in physical function at 24 weeks as measured by the TUG test. Worsening is defined as an increase of at least 1 second in TUG time from baseline. A 10% drop-out rate is assumed.

## 9.3 Populations for Analyses

For the purposes of the analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled | All participants who sign the ICF |
| Full analysis set (FAS) | All enrolled participants or all randomized patients (for the randomized portion of the study). This population will be used for baseline and disposition summaries as well as for the analysis of secondary endpoints related to efficacy. |
| Safety population | All enrolled (or randomized for the randomized portion of the study) participants who received any quantity of study intervention, regardless of their eligibility for the study. The safety evaluation will be performed based on the intervention actually received.<br>The safety population will be used for all baseline, exposure, physical function, cognitive function, daily function, and safety analyses. For the evaluation of each endpoint using an instrument or questionnaire, participants with baseline and at least one post-baseline assessment will be included. |

## 9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All variables will be analyzed with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e., mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

The primary analysis for the lead-in phase of the study will occur when the last participant has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. The primary analysis for the randomized phase of the study will occur when the last participant has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. The final analysis for the randomized phase of the study will occur when the last participant has been on the study for at least 52 weeks after the start of study intervention, unless the participant discontinued due to lost to follow-up, withdrawal, or death. Separate analyses will be performed for the lead-in phase and the randomized phase of the study. Participants will not be pooled across the two phases of the study.

### 9.4.1 Efficacy Analyses

| Endpoint | Statistical Analysis |
|---|---|
| Primary | There is no primary efficacy endpoint in this study. |
| Secondary | The study is not powered to test a specific hypothesis for efficacy, therefore, the two arms will not be formally compared for efficacy.<br>• The time to PSA progression will be calculated as the time from randomization (or the date of the first dose for participants in the lead-in phase) to the time when the criteria for PSA progression according to PCWG3. The PCWG3 guideline defines PSA progression as the date that an increase of 25% or more and absolute increase of 2 ng/mL or more from the nadir are documented. For participants who had an initial PSA decline during treatment, this must be confirmed by a second value 3 or more weeks later. Kaplan-Meier methods will be used to estimate the median time to PSA progression and 95% CIs for each treatment arm.<br>• Overall survival is defined as the time from the date of randomization (or the date of the first dose for participants in the lead-in phase) to death due to any cause. Participants who did not die will be censored at the date known to be alive. The Kaplan-Meier method will be used to estimate the median survival and survival rate at the 1-year time-point along with the 95% CI for each treatment arm. |
| Other pre-specified | Will be described in the statistical analysis plan |

### 9.4.2 Safety Analyses

All safety analyses will be performed on the Safety population.

Endpoints measuring physical function, cognitive function, and daily activity will also be performed on the Safety population.

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Primary** | The primary variable in this study is the proportion of participants with a worsening in TUG time during the 24-week period from baseline. Worsening is defined as an increase of at least 1 second in TUG time from baseline by 24 weeks.<br>• At each assessment, change in TUG test time (seconds) from baseline will be calculated, and the status will be categorized as: improved, stable, or declined using the MCID of 1 second. Decline in physical function is defined as at least a 1-second increase from baseline in TUG time in each arm by 24 weeks. The proportion of participants with a decline and the 95% CIs will be summarized for each treatment arm. This rate will be compared between the two arms using Cochran-Mantel-Haenszel test adjusting for stratification factors as captured by IWRS. |
| **Secondary** | **Physical Function**<br>• Proportion of participants with an increase of at least 1 second in the TUG time from baseline at 12 and 24 weeks, and by 52 weeks will be summarized similar to the primary endpoint.<br>• Time to worsening (increase of at least 1 second) in TUG time will be defined as time from randomization (or time from first dose for participants in the lead-in phase) to the first date a participant had an increase of at least 1 second or more from baseline. Time to worsening in TUG time will be summarized using Kaplan-Meier methodology, and a comparison between the two arms will be made using a two-sided, stratified log-rank test, stratified by IWRS strata. The hazard ratio as well as its 95% CI will be presented using a stratified Cox regression model. An unstratified analysis will also be performed.<br>• Similar to the primary endpoint, the proportion of participants with a decline of at least 0.5 points in SPPB total score at 12 and 24 weeks and by 24 and 52 weeks will be summarized.<br><br>**Daily Activity**<br>• Mean change from baseline in daily activity will be calculated for each treatment arm at 12 and 24 weeks, and by 24 weeks and 52 weeks and will be compared using two sample t-test. 95% CI will be presented.<br>• Mean change from baseline in accelerometer-assessed proportion of time spent in light to vigorous physical activity based on a threshold of >100 activity counts per minute at 12 and 24 weeks and by 24 and 52 weeks will be summarized.<br>Additional daily activity parameters based on accelerometry data may be explored and details will be provided in the SAP.<br><br>**Cognitive Function**<br>• The proportion of participants with a decline in cognitive function by 24 and 52 weeks as assessed by HVLT-R, TMT, and COWA, will be summarized similar to the primary endpoint. At each assessment, the change in score from baseline will be calculated and the status of cognitive function will be categorized as improved, stable, or declined using the Reliable Change Index (RCI) as shown below. Each test will be assessed individually. |

| Endpoint | Statistical Analysis Methods |
|---|---|

| Test | Reliable Change Index threshold (from baseline) |
|---|---|
| Hopkins Verbal Learning Test - Revised Total Recall (HVLT-R TR) | ±5 words |
| Hopkins Verbal Learning Test - Revised Delayed Recall (HVLT-R DR) | ±3 words |
| Hopkins Verbal Learning Test - Revised Delayed Recognition (HVLT-R RECOG) | ±2 words |
| Trail Making Test: Part A (TMTA) | ±12 seconds |
| Trail Making Test: Part B (TMTB) | ±26 seconds |
| Controlled Oral Word Association (COWA) | ±12 words |

- The proportion of participants with a decline of >10 points from baseline in the FACT-Cog domain by 24 and 52 weeks will be summarized.

**Fatigue**

- The proportion of participants with an increase of at least 1 point in worst level of fatigue from baseline during the past 24 hours (item 3 of BFI) by 24 and 52 weeks will be summarized.
- Similarly, the proportion of participants with an increase of at least 1 point in in fatigue interference from baseline during the past 24 hours (items 4A through F of BFI) by 24 and 52 weeks will be summarized. The proportion of participants with a decline and the 95% CIs will be summarized for each treatment arm. This rate will be compared between the two arms using Cochran-Mantel-Haenszel test adjusting for stratification factors as captured by IWRS.

**Depression**

- The proportion of participants with a worsening of scores by PHQ-9 during the 24 and 52 week period from baseline will be summarized. Worsening is defined as an increase of at least 1 point in worst level of depression from baseline by 24 weeks and 52 weeks.

**AE, Exposure, other**

- AEs, drug-related AEs, and SAEs will be summarized by MedDRA coding system and NCI-CTCAE version 5.0 worst grade.
- AE of interest (fall, fracture, hypothyroidism) will be summarized descriptively.
- Time to deterioration of KPS will be calculated as the time from randomization (or time from first dose for participants in the lead-in phase) to the first date the participant had a decline in KPS score of at least 10 points. Data will be summarized using the Kaplan-Meier method.
- Treatment exposure of the study intervention, including time on treatment and dose reductions, will be summarized.

### 9.5 Interim Analyses

No formal interim analyses are planned in this study. However, this study will be conducted in two phases and the primary analysis for the lead-in phase will be performed when the last participant in the lead-in phase has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. The decision to move to the randomized phase of the study will involve reviewing the findings from the lead-in phase of the study with the members of the steering committee.

The primary analysis for the randomized phase for the study will occur when last participant in the randomized phase of the study has been on the study for at least 24 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. A final analysis for the randomized phase for the study will occur when last participant in the randomized phase of the study has been on the study for at least 52 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death.

#### 9.5.1 Data Monitoring Committee (DMC)

Not applicable.

## 10. Supporting Documentation and Operational Considerations

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

#### 10.1.1 Regulatory and Ethical Considerations

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

### 10.1.2 Financial Disclosure

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

All relevant documentation will be filed in the trial master file.

### 10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A participant who is rescreened is required to sign another 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 that would make the participant identifiable will not be transferred.
- The participant must be informed that his 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.
- The participant must be informed that his 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

A steering committee will provide strategic direction, guidance and oversight for the study. This committee will meet approximately once a year or as required to keep track of issues and the progress of the study's implementation and activity.

No data monitoring committee, dose escalation committee, or similar review group will be used for this study.

### 10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents should be retained for the longer of the two periods prescribed below:
    - Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

### 10.1.7 Source Documents

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

### 10.1.8 Study and Site Closure

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

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

For any of the above closures, the following applies:

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

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

### 10.1.9 Publication Policy

The sponsor adheres to Good Publication Practice and authorship established by the International Committee of Medical Journal Editors (ICMJE). A Publication Roles and Responsibilities letter will be sent from Datavision, a publication management platform, to all authors for acknowledgement for each publication related to this study. For reference, the content of the letter can be found below. These roles and responsibilities are aligned with the sponsor’s corporate publication policy.

**Publication Roles and Responsibilities Letter:**

Bayer is committed to adhering to the prevailing standards for Good Publication Practice (GPP3) (Battisti et al. 2015) as well as the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE).

The purpose of this letter is to inform you about the roles and responsibilities of you, as an author, and Bayer, as sponsor:

**Author Responsibilities**

1. In accordance with the ICMJE authorship criteria, you must meet all of the following criteria to be considered an author of the publication:
   a. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
   b. Drafting the work or revising it critically for important intellectual content; AND
   c. Final approval of the version to be published; AND
   d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

   Authorship will be rescinded if you fail to meet all of the above requirements.
2. Contributors who do not meet the above criteria but who contributed to the publication, e.g., those who provided editorial assistance, writing support, statistical support, or study support, may be listed in the acknowledgements, with their permission.
3. You will develop publications which are accurate, objective and complete, in a timely and responsible manner.
4. You will comply with all applicable disclosure requirements, and will disclose any potential conflicts of interest.
5. You (and any other author) retain full editorial control over the content of the manuscript.
6. You (and any other author) accept full responsibility for final approval of the manuscript prior to submission.
7. You agree to comply with all applicable laws, regulations, industry codes and professional standards.
8. You represent that you have obtained all necessary approvals including from your institution or employer in connection with this publication.
9. You represent that you have not been debarred, disqualified, blacklisted or banned or to the best of your knowledge currently under investigations or threat of investigation by any regulatory authority for debarment, disqualification, blacklisting or any similar regulatory action in any jurisdiction anywhere in the world. During the term of this Agreement, you shall promptly notify Bayer should you become subject of such debarment, disqualification, blacklisting or banning proceeding.

**Bayer Responsibilities**

1. Bayer, upon request, will provide data, documents, and materials necessary for development of the manuscript/publication (under a standard confidentiality agreement).

2. Bayer may review the draft publication for scientific and medical accuracy. You (and any other author) will consider any comments made by Bayer in good faith, but may accept or reject revisions suggested by Bayer.

## 10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing: not applicable

**Table 10–1 Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet count<br>RBC count<br>Hemoglobin<br>Hematocrit | RBC indices:<br>MCV<br>MCH<br>% reticulocytes | WBC count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry | BUN | Potassium | AST/SGOT | Total and direct bilirubin |
| | Creatinine | Sodium | ALT/SGPT | Total protein |
| | Glucose (non-fasting) | Calcium | Alkaline phosphatase | |
| Routine urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Other screening tests | • Testosterone<br>• PSA<br>• TSH<br>The results of each test must be entered into the CRF. | | | |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRF = case report form; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; PSA = prostate-specific antigen; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell

Investigators must document their review of each laboratory safety report.

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

### 10.3.1 Definition of AE

| AE Definition |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study |

| AE Definition |
|---|
| participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br>• 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 intervention. |

| Events Meeting the AE Definition |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an 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.<br>• 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.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

### 10.3.2 Definition of SAE

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

**An 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 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 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 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**

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and graded using NCI-CTCAE version 5.0.

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 intervention 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 intervention administration will be considered and investigated.
- The investigator will also consult the 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 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.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

| **Assessment of Causality** |
|---|
| assessment.<br>• 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 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.<br>• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.<br>• New or updated information will be recorded in the originally completed CRF.<br>• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information. |

### 10.3.4 Reporting of SAEs

| **SAE Reporting to the Sponsor via an Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.<br>• 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.<br>• The site will enter the SAE data into the electronic system as soon as it becomes available.<br>• 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.<br>• 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 safety at the vendor by telephone.<br>• Contacts for SAE reporting can be found in the Investigator site file. |

| **SAE Reporting to the Sponsor via Paper CRF** |
|---|
| • Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to safety at the vendor.<br>• 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.<br>• Initial notification via telephone does not replace the need for the investigator to |

| **SAE Reporting to the Sponsor via Paper CRF** |
| --- |
| complete and sign the SAE CRF pages within the designated reporting time frames.<br>• Contacts for SAE reporting can be found in the Investigator site file. |

## 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

**Contraception Guidance for women of childbearing potential:** (see Inclusion criterion 3, Section 5.1)

The investigator or a designated associate is requested to advise the participant how to achieve highly effective birth control in women of childbearing potential. Highly effective (failure rate of less than 1% per year) contraception methods include:

- Combined (estrogen and progesterone containing: oral, intravaginal, transdermal) and progesterone-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion or vasectomized partner (provided that the partner is the sole sexual partner and has received medical assessment of the surgical success).
- Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant).

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

**Collection of Pregnancy Information**

Male participants with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, 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. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

## 10.5 Appendix 5: Abbreviations

| | |
|---|---|
| ADT | Androgen deprivation therapy |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AR | Androgen receptor |
| AST | Aspartate aminotransferase |
| AUC(0–24) | Area under the curve from time zero to 24 hours after dosing |
| BCRP | Breast cancer resistance protein |
| BFI | Brief Fatigue Inventory |
| bid | Twice daily |
| BUN | Blood urea nitrogen |
| CFR | Code of federal regulations |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| Cmax | Maximal plasma exposure |
| CNS | Central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| COWA | Controlled Oral Word Association |
| CPM | Counts per minute |
| CRF | Case report form |
| CRPC | Castration-resistant prostate cancer |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| DMC | Data monitoring committee |
| DRE | Disease-related event |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| F876L | Mutation of phenylalanine at position 876 to leucine |
| FACT-Cog | Functional Assessment of Cancer Therapy – Cognitive |
| FAS | Full analysis set |
| GCP | Good clinical practice |
| GMP | Good manufacturing practice |
| GnRH | Gonadotropin-releasing hormone |
| GPP3 | Good publication practice 3 |
| HDPE | High density polyethylene |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HVLT-R | Hopkins Verbal Learning Test – Revised |
| HVLT-R DR | Hopkins Verbal Learning Test – Revised Delayed Recall |
| HVLT-R RECOG | Hopkins Verbal Learning Test – Revised Delayed Recognition |
| HVLT-R TR | Hopkins Verbal Learning Test – Revised Total Recall |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |

| | |
|---|---|
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| IWRS | Interactive web response system |
| KPS | Karnofsky Performance Scale |
| LHRH | Luteinizing hormone-releasing hormone |
| LPLV | Last patient last visit |
| MCH | Mean corpuscular hemoglobin |
| MCID | Minimal clinically important difference |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFS | Metastasis-free survival |
| MRI | Magnetic resonance imaging |
| NCI | National Cancer Institute |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NIMP | Non-investigational medicinal product |
| NJ | New Jersey |
| OS | Overall survival |
| PCWG | Prostate Cancer Working Group |
| PE | Polyethylene |
| PFS | Progression-free survival |
| PHQ-9 | Patient Health Questionnaire-9 |
| PK | Pharmacokinetic |
| PP | Polypropylene |
| PRIME-MD | Primary Care Evaluation of Mental Disorders |
| PSA | Prostate-specific antigen |
| QOL | Quality of life |
| RBC | Red blood cell |
| RCI | Reliable change index |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SGOT | Serum glutamic-oxaloacetic transaminase |
| SGPT | Serum glutamic-pyruvic transaminase |
| SID | Subject identification |
| SmPC | Summary of product characteristics |
| SoA | Schedule of activities |
| SPPB | Short Physical Performance Battery |
| SSE-FS | Symptomatic skeletal event-free survival |
| SUSAR | Suspected unexpected serious adverse reactions |
| TEAE | Treatment-emergent adverse event |
| TMT | Trail-Making Test |
| TMTA/TMTB | Trail Making Test Part A/B |
| TSH | Thyroid-stimulating hormone |
| TUG | Timed Up & Go |
| ULN | Upper limit of normal |
| USA | United States of America |
| WBC | White blood cell |

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